# INCIDENCE OF SURGICAL WOUND INFECTION IN ENGLAND AND WALES

**A report of the Public Health Laboratory Service**

THERE is a general impression that postoperative wound sepsis is becoming more common. This belief is probably based on reports of outbreaks of exceptional severity, with sepsis-rates between 10% and 37%, and effects on patients varying from negligible inconvenience to profusely discharging sinuses and death; or from a few extra days to many months in hospital. These figures from outbreaks of infection are probably reliable because they were collected at times when the units concerned were "sepsis conscious" and all the manifestations of wound infection were carefully noted. Attempts to determine sepsis-rates in non-epidemic times have been less satisfactory. General inquiry of hospitals yields widely divergent answers. Some admit that they are uneasy about sepsis, whilst others stoutly deny that it occurs at all. Retrospective analysis of clinical records is almost useless because only sepsis of the grossest kind is recorded in them. It thus appears that only an investigation planned for the specific purpose can yield a true estimate of the general frequency and cost of wound sepsis.

A few investigations of this type have already been made in single hospitals. In Britain, Clarke (1957) reported a sepsis-rate of 13·6%, causing a mean extra stay in hospital of 8·1 days; Jeffrey and Sklaroff (1958) found that sepsis developed in 26·1% of clean operation wounds, and that this was "serious" in 9·8%; Burnett et al. (1958) recorded a sepsis-rate of 7·6%. There are similar reports from Australia, Canada, and the United States.

These reports suggest that sepsis-rates throughout the country may be much higher than is generally realised. The present investigation was therefore planned to give information on the incidence of wound sepsis and its cost in terms of loss of life and length of stay in hospitals where there is no special complaint of sepsis. This was the main object of the investigation, but the opportunity was taken to determine the relationship between wound sepsis and some of the circumstances that might determine its development. These were nasal carriage of *Staphylococcus aureus* by the patient before operation, age and sex, nature and duration of the operation, length of incision, and presence or absence of a drainage tube.

## Methods

*General Plan of the Investigation*

The hospitals studied were selected on the basis of convenience and not because of any special concern over the incidence of sepsis. For the main survey all were hospitals for which one of the laboratories of the Public Health Laboratory Service carried out the routine bacteriology, and in each centre the investigation was supervised jointly by the bacteriologist and one or more of the surgeons.

There were three phases of the study:

1. *A pilot survey* in four hospitals, lasting one month during the summer of 1957, which demonstrated the practicability of the general plan and revealed the need for some small but important changes of procedure.

2. *The main survey* from August, 1957, to April, 1959. Eleven hospitals took part, though not all for the whole period; but nine kept records for at least twelve months.

3. *A short survey.*—During one week in the last month of the trial, the results of the main participants were supplemented by those from nine other hospitals. This was intended as a check on the results of the main survey and to give the whole investigation a wider geographical representation.

*Selection of Patients*

In each unit, the patients included in the survey were all whose operation involved an incision through healthy skin, except those operated on because of sepsis—such as incision of an abscess or drainage of an empyema. Operations on the lower urinary tract, rectum, or anus and on accidental wounds were excluded, not because sepsis in them was thought to be any less important but because infection added in hospital is easier to recognise in previously clean wounds, which were therefore used as the most convenient indicators of hospital infection. Patients with appendix abscess and those with other abdominal disease who were found to have peritonitis at the time of operation, mostly due to perforated duodenal ulcers, were included but are presented separately in several of the tables.

*Records*

Records were kept for each patient on a special form.

*On the day of admission to hospital* a nose swab was taken from each patient and was cultured for *Staph. aureus* and *Streptococcus pyogenes* by direct and enrichment methods. If more than a week elapsed before the operation, the nose was swabbed again on the day of operation. All strains isolated were stored and most strains of *Staph. aureus* were submitted for phage typing.

*Immediately after the operation* the surgeon recorded details of it and his estimate of the time the patient would be in hospital.

*During the postoperative period* the wound was examined at the time of the first dressing, then weekly, or more often if abnormalities were noticed, and then again on the day of discharge from hospital. For a great many operations the wound was in fact examined only once because the postoperative dressing was not removed until the wound was healed and the patient ready for discharge. The state of the wound was recorded at each examination by the surgeon, bacteriologist, ward sister, registrar, or resident doctor, but efforts were made to ensure that at least half of the wounds, and all those not healing normally, were seen by the surgeon or bacteriologist.

Swabs were taken from nearly all wounds at the time of the first dressing and at any later examination if they were not healing cleanly. All organisms isolated were noted in the postoperative record. Strains of *Staph. aureus* from wounds were typed.

*After the patient's discharge from hospital*, the surgeon and bacteriologist jointly decided whether there was clinical and bacteriological evidence of infection.

## Results

From the pilot and main surveys in twelve hospitals we had records for 3002 operations, and from the short survey in some of these and in the ten other hospitals we had a further 274. Since the results from the three surveys were very similar, most of the analyses presented here are based on the total of 3276 operations. Clinical records were available for them all, though they were

TABLE I—INCIDENCE OF SEPSIS AND INFECTION WITH PATHOGENIC BACTERIA (ALL WOUNDS WITH BACTERIOLOGICAL RESULTS AVAILABLE EXCEPT THOSE IN PATIENTS WITH PERITONITIS)

| Clinical state of wound | Wounds | | Pathogenic bacteria isolated from wound during convalescence | | | | | No. in which pathogens isolated |
|---|---|---|---|---|---|---|---|---|
| | | | *Staph. aureus* | | Coliform organisms alone | Other pathogenic bacteria | Total | |
| | No. | % of total | Alone | With other pathogens (mainly coliforms) | | | | |
| Healthy | 2366 | 86 | 188 | 14 | 106 | 47 | 355 | 2011 |
| Septic | 380 | 14 | 172 | 57 | 65 | 14 | 308 | 72 |
| Discharging pus | 182 | 6·6 | 96 | 37 | 31 | 7 | 171 | 11 |
| Serous discharge, gaping, healing by granulation, or general erythema; never purulent | 139 | 5·1 | 54 | 18 | 26 | 4 | 102 | 37 |
| Stitch abscess only | 19 | 0·7 | 10 | 1 | 3 | 2 | 16 | 3 |
| Marginal erythema only | 40 | 1·5 | 12 | 1 | 5 | 1 | 19 | 21 |
| All wounds | 2746 | 100 | 360 | 71 | 171 | 61 | 663 | 2083 |

not invariably complete in every detail; 403 of the 2840 clinically healthy and 13 of the 436 clinically septic wounds were not examined bacteriologically. There were 58 patients who had an appendix abscess and 56 others who were found to have peritonitis at operation; these have been excluded from tables I and IV.

We have used the term " septic " to refer to clinically manifest disease in the wound, and " infected " to mean the presence of pathogenic bacteria, including as pathogens coagulase-positive staphylococci, hæmolytic streptococci, fæcal streptococci, and coliform bacilli. Included in the coliform group were *Escherichia coli*, *Klebsiella* species, *Proteus* species, and paracolon bacilli.

*General Incidence of Sepsis and Infection*

Of the 2746 wounds (excluding those in patients with peritonitis) for which we had complete clinical and bacteriological information, 380 (14%) showed some signs of sepsis during healing and 663 (24%) yielded pathogenic bacteria on culture (table I); 308 (11% of the total) were septic and yielded pathogenic bacteria. Because it was very largely the healthy wounds for which bacteriological records were not available this last rate, when calculated on the whole population (i.e., including those not examined bacteriologically), was slightly lower (9·7%).

Almost half the wounds reported as septic discharged pus at some time and only 59 (16%) had no more than a stitch abscess or marginal erythema. Pathogenic bacteria were found in 308 (81%) of the 380 septic wounds and in 171 (94%) of the 182 purulent wounds. *Staph. aureus* was found in 229 (60%) of the septic wounds and in 202 (9%) of the healthy wounds.

After *Staph. aureus*, the commonest pathogens in septic wounds were coliform organisms, which occurred together with staphylococci in 50 (13%) and alone in 65 (17%).

Nine hospitals contributed records of 100 or more wounds to the main survey (table II); but two of them (A and B), in one city, contributed nearly half the total.

TABLE II—SEPSIS-RATES BY HOSPITALS

| Hospital | Total no. of patients (1) | % of total clinically septic (2) | % septic and infected with pathogens (3) | % examined and healthy but infected with pathogens (4) |
|---|---|---|---|---|
| A | 816 | 13·0 | 11·4 | 17·0 |
| B | 736 | 13·9 | 12·9 | 16·7 |
| C | 316 | 8·9 | 4·7 | 14·9 |
| D | 308 | 13·3 | 9·7 | 6·9 |
| E* | 166 | 1·8 | 1·2 | 3·8 |
| F | 165 | 9·7 | 7·9 | 33·9 |
| G† | 164 | 12·8 | 9·1 | 9·9 |
| H | 110 | 26·4 | 21·8 | 29·6 |
| I | 102 | 21·6 | 12·7 | 6·3 |
| J | 55 | 23·6 | 16·4 | 16·7 |
| K | 51 | 9·8 | 7·8 | 6·5 |
| L‡ | 13 | 7·7 | 7·7 | 25·0 |
| Totals: main survey | 3002 | 12·9 | 10·5 | 15·0 |
| short survey | 274 | 17·9 | 11·3 | 15·4 |
| Aggregate | 3276 | 13·3 | 10·6 | 15·1 |

Hospitals A and B are in the same city.
* Orthopædic operations only.
† Thoracic operations only.
‡ Took part in pilot survey only.

TABLE III—INCIDENCE OF SEPSIS AND INFECTION AFTER VARIOUS OPERATIONS (ALL PATIENTS)

| Operation | All patients | | | Patients with healthy wounds | | Patients with infected wounds: % with sepsis |
|---|---|---|---|---|---|---|
| | No. (1) | % with sepsis and infection (2) | % with staphylococcal sepsis (3) | No. examined bacteriologically (4) | % infected with pathogens (5) | (6) |
| Gallbladder | 247 | 20·6 | 14·9 | 172 | 17·4 | 63·0 |
| Breast | 188 | 15·4 | 12·7 | 122 | 6·6 | 78·4 |
| Miscellaneous abdominal | 373 | 12·9 | 11·0 | 275 | 18·5 | 48·5 |
| Varicose veins | 179 | 11·7 | 8·9 | 98 | 24·5 | 46·7 |
| Thorax | 171 | 8·8 | 7·5 | 148 | 10·1 | 50·0 |
| Gastrectomy | 240 | 8·7 | 5·8 | 189 | 17·6 | 38·9 |
| Sympathectomy | 39 | 7·7 | 7·7 | 31 | 12·9 | 42·9 |
| Hernia | 437 | 7·3 | 5·9 | 348 | 21·3 | 30·2 |
| Appendix | 550 | 6·7 | 2·3 | 415 | 9·4 | 48·7 |
| Thyroid | 165 | 4·2 | 3·6 | 140 | 12·9 | 28·0 |
| Miscellaneous orthopædic | 208 | 2·9 | 2·9 | 165 | 4·9 | 42·9 |
| Meniscectomy | 64 | 0 | 0 | 62 | 8·1 | 0 |
| Miscellaneous | 301 | 12·0 | 10·6 | 200 | 23·0 | 43·9 |
| Appendix abscess | 58 | 43·1 | 22·4 | 31 | 22·6 | 78·1 |
| Other abdominal with peritonitis | 56 | 21·4 | 10·7 | 40 | 12·5 | 70·6 |

The incidence of septic infected wounds varied between 21·8% and 1·2%. The latter figure was from an orthopædic service; the lowest figure in a general hospital was 4·7%. There were some curious differences in the proportions of infected but healthy wounds (column 4) which we have not been able to explain; they were not due to obvious differences in technique.

No consistent seasonal differences could be detected.

*Incidence of Sepsis and Infection after Different Operations*

Table III shows the proportions of the wounds that were both infected and septic (column 2) or infected but clinically healthy (column 5) for the various categories of operation. Only three categories had sepsis-rates below 5%, and four (other than those with peritonitis) had rates over 10%. The highest rates were, not unexpectedly, in the two groups of patients with peritonitis present at operation, for which " sepsis " refers to disease in the parietal wound; but clean gallbladder operations had a

TABLE IV—INCIDENCE OF SEPSIS AND INFECTION IN RELATION TO VARIOUS FACTORS (ALL PATIENTS EXCEPT THOSE WITH PERITONITIS)

| — | All patients | | Patients with healthy wounds | | Patients with infected wounds: % septic |
|---|---|---|---|---|---|
| | No. | % with sepsis and infection | No. examined bacteriologically | % infected | |
| *Sex:* | | | | | |
| Male | 1619 | 10·3 | 1232 | 17·4 | 43·7 |
| Female | 1540 | 9·3 | 1132 | 12·4 | 50·5 |
| *Age (yr):* | | | | | |
| 0–29 | 766 | 6·4 | 566 | 11·8 | 42·2 |
| 30–59 | 1647 | 7·9 | 1256 | 14·7 | 41·3 |
| 60+ | 702 | 18·1 | 477 | 21·2 | 55·7 |
| *Length of incision (in.).* | | | | | |
| 0–6 | 2189 | 6·9 | 1672 | 14·9 | 37·6 |
| More than 6 | 887 | 16·3 | 632 | 15·2 | 60·2 |
| *Duration of operation (min.):* | | | | | |
| 0–30 | 1102 | 4·3 | 848 | 9·9 | 35·9 |
| 31–60 | 1086 | 9·8 | 813 | 16·1 | 44·7 |
| 61+ | 729 | 17·7 | 511 | 20·7 | 54·9 |
| *Drainage:* | | | | | |
| Not inserted | 2260 | 6·7 | 1727 | 14·2 | 51·0 |
| Inserted | 885 | 16·5 | 633 | 17·2 | 57·2 |
| *Total* | 3162 | 9·7 | 2366 | 15·0 | 46·4 |

Totals for the separate classifications do not agree because individual items of information were missing from some records.

rate nearly as high. In all categories but one, symptomless infection had an incidence rather higher than clinical sepsis, but in the four categories with the high sepsis-rates sepsis developed in most of the wounds that became infected.

*Various Factors Correlated with Sepsis*

The differences in sepsis-rates between the operations must to some extent reflect differences in the types of patient who needed the various operations, and also the nature of the operation itself. Five such factors are analysed in table IV, which refers to all patients other than those with pre-existing peritonitis. Increasing age, length of incision, and duration of operation were all associated with an increase in sepsis-rate. Sepsis developed more often in drained wounds than in undrained. The incidence of asymptomatic infection showed the same trends but to a lesser degree.

The different factors analysed in table IV are clearly interrelated; old people tended to have operations of longer duration than young; long incisions were more often drained than short; and so on. More complex statistical analysis by Dr. O. M. Lidwell (to be published elsewhere) suggested that each of four factors—age, length of incision, duration, and drainage—had an independent effect in leading to an increased sepsis-rate.

*Type of Infection in Various Operation Wounds*

Although *Staph. aureus* was the predominant pathogen it was not equally common in the septic wounds of different types of operation (table V). Coliform infections were particularly common after operations in the abdominal cavity, but they were by no means confined to these operation wounds. The proportion having pure coliform infections was also higher in the clinically healthy than in the septic wounds.

*Relation of Staphylococcal Infection to Nasal Carriage*

Nasal swabs showed 821 (27%) patients to be carriers of *Staph. aureus*; 8·9% of the carriers showed staphylococcal sepsis of their wounds during convalescence, compared with 7·1% of the non-carriers (table VI). This difference is not statistically significant (S.E. diff. = 1·06).

Of the 601 patients who had staphylococci of a defined type in their nose (i.e., excluding the 94 with untypable strains and the 126 whose strains were not sent for typing), 63 (10·5%) developed staphylococcal sepsis; in 24 (4·0%) the staphylococcus from the wound was the same type as that in the nose and in 36 (6·0%) it was different; in the remaining 3 the phage-type comparison was inconclusive.

TABLE VI—RELATION OF STAPHYLOCOCCAL SEPSIS TO NASAL CARRIAGE

| — | Patients with: | | | |
|---|---|---|---|---|
| | *Staph. aureus* in nose (821 patients) | | No *Staph. aureus* in nose (2235 patients) | |
| | Sepsis at 1st dressing | Sepsis later | Sepsis at 1st dressing | Sepsis later |
| *No. with staphylococcal sepsis* | 51 | 22 | 103 | 55 |
| *No. with wound staphylococcus:* | | | | |
| Same as nose strain | 22 (*43%*) | 2 (*9%*) | — | — |
| Doubtfully same nose strain | 3 (*6%*) | 0 | — | — |
| Different from nose strain | 23 (*45%*) | 13 (*59%*) | — | — |
| Not typed | 3 (*6%*) | 7 (*32%*) | — | — |
| *Total sepsis* | 73 (*8·9%*) | | 158 (*7·1%*) | |

Nasal carriers of a few phage types of staphylococci appeared to have an above-average risk of self-infection. Thus, of the 74 who carried strains of types 80, 52/52A/80, or 52/80 in the nose before operation, postoperative sepsis developed in 11 (14·9%), in 10 cases with a staphylococcus of the type found in the nose.

Staphylococci of phage-group II, and of the miscellaneous groups were rare in the septic wounds (table VII); it was not therefore surprising that no nasal carriers

TABLE V—BACTERIA RESPONSIBLE FOR SEPSIS AND INFECTION IN VARIOUS OPERATION WOUNDS (ALL WOUNDS WITH PATHOGENIC BACTERIA)

| Operation | Septic wounds | | | | | Healthy wounds | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | No. | % with: | | | | No. | % with: | | | |
| | | *Staph. aureus* total | *Staph. aureus* alone | Coliforms alone | Other pathogens | | *Staph. aureus* total | *Staph. aureus* alone | Coliforms alone | Other pathogens |
| Miscellaneous orthopædic | 6 | (100·0) | (66·7) | 0 | 0 | 8 | (75·0) | (75·0) | (25·0) | 0 |
| Sympathectomy | 3 | (100·0) | (100·0) | 0 | 0 | 4 | (100·0) | (75·0) | 0 | 0 |
| Thorax | 15 | 86·7 | 66·7 | 13·3 | 0 | 15 | 80·0 | 66·7 | 13·3 | 6·7 |
| Thyroid | 7 | (85·7) | (85·7) | (15·3) | 0 | 18 | 77·7 | 72·2 | 22·2 | 0 |
| Miscellaneous abdominal | 48 | 85·4 | 54·2 | 10·4 | 4·2 | 51 | 56·9 | 56·9 | 33·3 | 9·8 |
| Breast | 29 | 82·7 | 72·4 | 13·8 | 3·4 | 8 | (75·0) | (62·5) | (25·0) | 0 |
| Hernia | 32 | 80·2 | 68·7 | 15·6 | 3·1 | 74 | 58·0 | 54·0 | 29·7 | 25·7 |
| Varicose veins | 21 | 76·2 | 42·9 | 23·8 | 0 | 24 | 41·6 | 33·3 | 58·3 | 0 |
| Gallbladder | 51 | 72·5 | 58·8 | 23·5 | 3·9 | 30 | 66·6 | 63·3 | 20·0 | 13·3 |
| Gastrectomy | 21 | 66·6 | 47·6 | 19·0 | 14·3 | 33 | 69·7 | 66·7 | 15·1 | 15·1 |
| Appendix | 37 | 35·1 | 16·2 | 56·8 | 8·1 | 39 | 33·3 | 33·3 | 46·1 | 20·5 |
| Appendix abscess | 25 | 52·0 | 24·0 | 44·0 | 4·0 | 7 | (14·3) | (14·3) | (85·7) | 0 |
| Miscellaneous abdominal with peritonitis | 12 | 50·0 | 16·7 | 16·7 | 33·3 | 5 | (40·0) | 0 | (40·0) | (20·0) |
| Miscellaneous | 38 | 88·2 | 65·8 | 15·8 | 5·3 | 46 | 65·2 | 60·9 | 26·1 | 8·7 |

Percentages based on less than 10 patients are in parentheses.

TABLE VII—PERCENTAGE PHAGE-TYPE DISTRIBUTION OF STAPHYLOCOCCI FROM WOUNDS

| Phage group and type | Hospitals other than A and B | | Hospitals A and B | | No. of hospitals with type represented |
|---|---|---|---|---|---|
| | Septic | Healthy | Septic | Healthy | |
| *I:* | | | | | |
| 80 .. .. .. | 25·9 | 13·7 | 10·1 | 11·0 | 10 |
| 52/52A/80; 52/80* .. | 6·2 | 5·3 | 47·3 | 43·8 | 6 |
| 29 .. .. | 1·2 | 10·5 | 1·4 | 1·4 | 8 |
| 29/52/80 &c. .. | 6·2 | 3·2 | 0·7 | 1·4 | 6 |
| Others .. .. | 7·4 | 3·2 | 6·1 | 5·5 | .. |
| Total .. .. | 46·9 | 35·0 | 65·6 | 61·7 | .. |
| *II, total* .. .. | 1·2 | 8·4 | 4·7 | 5·5 | .. |
| *III:* | | | | | |
| 75/77 .. .. | 6·2 | 4·2 | 0·7 | 2·7 | 6 |
| 47/53/75/77 &c.† .. | 6·2 | 2·1 | 0 | 1·4 | 3 |
| 6/47/53/75 .. .. | 0 | 5·3 | 0·7 | 0 | 1 |
| 6/7/42E/47/53/54 &c. | 1·2 | 3·2 | 2·0 | 1·4 | 4 |
| 7/42E/47/53/54 .. | 1·2 | 2·1 | 1·4 | 1·4 | 3 |
| 77 .. .. .. | 2·5 | 0 | 2·0 | 0 | 4 |
| 53 .. .. .. | 2·5 | 0 | 2·0 | 0 | 3 |
| 75 .. .. .. | 3·7 | 0 | 0 | 0 | 2 |
| Others .. .. | 6·2 | 1·1 | 7·4 | 6·9 | .. |
| Total .. .. | 29·7 | 17·9 | 16·2 | 13·7 | .. |
| *Mixed, total* .. .. | 4·9 | 2·1 | 6·1 | 1·4 | .. |
| *Miscellaneous, 187* .. | 0 | 2·1 | 0 | 0 | 2 |
| *Untypable* .. .. | 17·3 | 33·7 | 7·4 | 17·8 | .. |
| *No. of wounds with staphylococci typed* .. | 81 100·0 | 95 100·0 | 148 100·0 | 73 100·0 | .. |

* Including a small number of strains reported as 80+.
† Including strains with the patterns 53/75/77, 47/75/77.

of such staphylococci showed sepsis apparently due to self-infection. For some unexplained reason, the 106 nasal carriers of group-II strains also had a very low (0·9%) cross-infection rate.

There is a suggestion, though the figures are small, that sepsis present at the time of first dressing was more commonly due to a staphylococcus found in the nose than was sepsis developing later (table VI). In a third of the cases of symptomless wound infection in nasal carriers, staphylococci from the wounds were of the same phage type as the nasal strain.

### *Interval between Admission to Hospital and Operation*

The sepsis-rate was higher for patients who were in hospital eight days or more before having their operation than for those who had the operation soon after admission (table VIII). We found no explanation for this but cannot exclude the possibility that delay in performing the operation is often associated with other factors that favour sepsis such as greater age of the patient and longer and more severe operations.

### *Phage Type of Staphylococci*

The phage types of staphylococci from the septic and healthy wounds are shown in table VII. Since a large proportion were derived from the wounds in two hospitals in one city, these have been presented separately. Phage-type 80 was by far the commonest type in the hospitals other than A and B, where strains with the related patterns 52/52A/80 and 52/80 were even more common. It was curious to observe that no type-80 strains were found in the wounds examined in five of the hospitals in the North of England; the type was found in all but one of the eleven contributing hospitals in the South and South West and Wales. Staphylococci of type 29 were much commoner in healthy than in septic wounds, as were untypable strains.

TABLE VIII—INTERVAL BETWEEN ADMISSION TO HOSPITAL AND OPERATION, IN RELATION TO SEPSIS

| Days in hospital before operation | No. of patients | % in whom staphylococcal sepsis developed |
|---|---|---|
| 0–2 | 2103 | 6·6 |
| 3–7 | 762 | 7·9 |
| 8+ | 388 | 11·9 |

### *Length of Stay in Hospital*

At the end of each operation the surgeon was asked to predict the patient's length of stay in hospital. We have tried to measure the consequences of sepsis by determining the difference between the expected stay and the actual stay. For this analysis we have excluded all patients who died, who were kept in hospital for any reason (medical or non-medical) not associated with wound healing, or who were transferred to a convalescent home before the wound was healed.

The results for the 2688 patients suitable for analysis are given in table IX. For those with healthy and uninfected wounds the surgeons' estimates were very accurate, the average stay in hospital being less than one day shorter than predicted. There was a suggestion that the apparently healthy but infected wounds may have suffered a slight delay in healing. There was also some delay with the septic wounds from which no pathogens were isolated; it will be remembered that most of these showed only rather trivial signs of sepsis (table I). The patients whose wounds were septic and infected with pathogens had a mean excess stay of 7·3 days; but within this group the discharging wounds had an excess of over 10 days, whereas stitch abscesses and marginal erythema were associated with less than 2 days' excess.

The predicted stay for the whole group of 2688 patients was 32,442 days; but, allowing for the fact that in uncomplicated cases the patients left hospital earlier than predicted, the total "uncomplicated" stay would actually have been 30,383 days if sepsis or infection had developed in no case. The excess of 1772 days due to the septic patients was thus 5·8% of the probable uncomplicated stay.

TABLE IX—LENGTH OF STAY IN HOSPITAL

| State of wound | | No. of patients with records available | Mean no. of days in hospital | | No. of days excess or deficit, for group |
|---|---|---|---|---|---|
| Clinical | Bacteriological | | Expected | Actual less expected | |
| Healthy | Not infected | 1736 | 11·8 | −0·766 | −1330 |
| ,, | Not known | 347 | 10·3 | −1·058 | − 367 |
| ,, | Infected | 306 | 13·2 | −0·203 | − 62 |
| Septic | Not infected | 58 | 13·8 | +1·155 | + 67 |
| ,, | Not known | 8 | 9·0 | +0·125 | + 1 |
| ,, | Infected | 233 | 14·9 | +7·313 | +1704 |
| Discharging pus .. | | 126 | 15·8 | +10·389 | +1309 |
| Granulation, exudate, &c. .. .. | | 80 | 13·5 | + 4·512 | + 361 |
| Stitch abscess only .. | | 14 | 15·3 | + 1·929 | + 27 |
| Marginal erythema only .. .. | | 13 | 15·1 | + 0·538 | + 7 |

The mean excess stays in days for the septic patients in various operation groups were as follows: appendix abscess 12·4, breast 9·2, appendix 8·1, gallbladder 6·1, hernia 5·8, gastrectomy 4·3, varicose veins 4·3. These are to be compared with the mean excess for all septic patients of 7·2 days. For the same set of patients pure staphylococcal sepsis was associated with an excess of 5·3 days, pure coliform sepsis with an excess of 6·5 days, and mixed staphylococcal and other pathogens (mostly coliforms) with an excess of 14·0 days.

*Deaths*

Altogether 58 (1·8%) of the patients in the survey died; 28 of those who died were 70 or more years old and 12 more were aged 60–70. The death-rate was higher in the patients in whom wound sepsis developed (4·1%) than in those in whom it did not (1·5%), but this was perhaps to be expected since sepsis developed more commonly in the old people. Our records of the cause of death were not sufficiently detailed, but it seemed that only 1 of the deaths could be attributed without question to wound sepsis. Besides this, there were a few in which the evidence was suggestive but not conclusive.

## Discussion

The aim of this investigation was to obtain a broadly based estimate of the amount of postoperative wound sepsis now occurring in hospitals in England and Wales. Though 1652 of the 3276 patients in the survey were in two hospitals in one city, the fact that their sepsis-rate was very close to that of the remaining 1624 patients in nineteen other hospitals justifies one regarding the incidence of sepsis—9·7% of all wounds—as a useful estimate of the figure for general hospitals. Almost half the patients with "septic" wounds had discharge of frank pus so that, even on this more restricted criterion, the incidence of sepsis would have been about 5%. Sepsis was not confined to the more complex operations, and even herniorraphies had a sepsis-rate of over 7%. These rates are much higher than many clinicians would regard as acceptable, and they seem to confirm the impression given by the local surveys, mentioned earlier, that surgical sepsis is commoner than most people have thought. Yet they probably underestimate the full problem because certain types of infection, such as those after surgery of the lower urinary tract, were excluded from the survey but are known to be very common.

Higher sepsis-rates are associated with older patients, larger incisions, longer operations, and the use of drainage tubes. Detailed statistical analysis to show that each of these has an independent effect will be presented elsewhere. They are not factors that can be controlled in an attempt to prevent sepsis, but it is important to know of their association with it so that allowance may be made for them when sepsis-rates from different surveys are being compared. The higher rates of sepsis in nasal carriers of some strains of staphylococci and in patients admitted to hospital a week or more before operation appear to deserve further study.

Measurement of the "cost" of sepsis is much more difficult. If our figures are applicable to the 1·5 million surgical operations performed annually in all hospitals in England and Wales, the total excess stay in hospital due to sepsis may be about 1,000,000 days per year, or about 3% of the total bed-occupancy of acute hospitals. The monetary cost of this may be about £3·3 million, or about 0·5% of the total cost of the National Health Service; and to this must be added the cost of sickness insurance, loss of wages, and so forth. But the obvious conclusion—that some £5 million might be saved by the elimination of sepsis—is not necessarily true, and indeed it may be necessary to spend more than £5 million each year if we are to make any substantial progress towards eliminating sepsis. It may be better to regard as a challenge to our medical skills the thought of 75,000 people who had clean operation wounds that discharged pus, of the 5000 whose stay in hospital was prolonged by a month or more, and of the, perhaps, 500 who died from sepsis.


## Summary

A survey was carried out to determine the incidence of sepsis after surgical operations and its cost in terms of excess stay in hospital. A total of 3276 surgical operations in twenty-one different hospitals were studied clinically, and (in 2860 cases) bacteriologically during convalescence.

9·7% of the wounds were affected by some post-operative sepsis and yielded pathogenic bacteria on culture. The sepsis-rate in different hospitals undertaking general surgery varied between 4·7% and 21·8%. The highest sepsis-rates after clean operations were for cholecystectomy (21%) and breast operations (15%), and the lowest were for orthopædic operations (2%).

Greater age of the patient, length of preoperative stay in hospital, length of incision, and duration of operation were all associated with increased sepsis-rates, as was the use of a drainage tube. *Staphylococcus aureus* was the commonest pathogen, but infection with coliform organisms was also common.

Nasal carriers of *Staph. aureus* had only a slightly higher postoperative-sepsis rate than non-carriers (8·9% compared with 7·1%), but nasal carriers of a few phage types of staphylococci had a considerably higher sepsis-rate.

Patients whose wounds healed without sepsis or infection left hospital, on average, 0·8 days earlier than had been predicted on the day of operation; those with sepsis and infection had an excess stay of 7·3 days over that predicted.

58 of the patients in the survey died, but in only 1 case was death definitely attributable to wound sepsis.



We are grateful to the clinicians who allowed this survey to be made in their wards and who, together with their nursing staff, kept many of the records that were needed for it. The following took part in the investigations in the hospitals:

*Surgeons and physicians.*—Mr. D. S. M. Barlow, Mr. J. P. Childs, Dr. W. Clancy, Mr. L. G. Cruickshank, Mr. J. E. H. Ellis, Mr. H. De, Mr. W. J. Fraser, Mr. E. W. Grahame, Mr. S. G. Griffin, Mr. F. M. Hanna, Mr. D. H. C. Harland, Mr. A. H. Haxton, Mr. R. M. Hill, Mr. P. W. Houghton, Mr. R. E. Isaac, Mr. B. Isserlin, Mr. M. Leitch, Mr. D. H. Lloyd, Mr. S. N. Lytle, Mr. K. C. McKeown, Mr. G. H. Marshall, Mr. F. Masina, Mr. H. Dendy Moore, Mr. C. P. Nicholas, Mr. F. J. P. O'Gorman, Mr. S. Pappworth, Mr. G. Parker, Dr. W. C. Pinkney, Mr. L. W. Plewes, Mr. T. Rountree, Mr. G. H. A. Simmons, Miss B. V. Slesser, Mr. D. J. Ross Steen, Mr. T. Russell Stevens, Mr. B. R. Sworn, Mr. B. Thomas, Mr. L. B. Williams, Mr. D. C. Williams.

*Bacteriologists.*—Dr. R. Blowers,* Dr. D. R. Christie,* Dr. P. B. Crone, Dr. D. G. Davies, Dr. E. H. Gillespie,* Dr. R. J. Henderson,* Dr. H. D. Holt, Dr. K. E. A. Hughes,* Dr. R. I. Hutchinson, Dr. C. H. Jellard,* Dr. E. M. Mackay-Scollay,* Dr. N. S. Mair,* Dr. B. Moore,* Dr. H. D. S. Morgan,* Dr. D. J. H. Payne, Dr. Lewis Parker, Dr. R. Pilsworth, Dr. H. G. Smith, Dr. J. W. G. Smith, Dr. Marjorie V. Sudds, Dr. G. H. Tee, Prof. Scott Thomson,* Dr. Margaret Wilson.

* The bacteriologists indicated with an asterisk, together with Dr. R. E. O. Williams and Dr. J. C. McDonald, constituted the working party that organised the investigation.

The results were analysed and the report was prepared by Dr. R. E. O. Williams, Dr. J. C. McDonald, and Dr. R. Blowers.

We are indebted to the Registrar General of England and Wales for estimates of the number of surgical operations performed each year.


### REFERENCES


Burnett, W., McDonald, S., Timbury, M. C. (1958) *Scot. med. J.* **3**, 392.
Clarke, S. K. R. (1957) *Brit. J. Surg.* **44**, 592.
Jeffrey, J. S., Sklaroff, S. A. (1958) *Lancet*, **i**, 365.

# HYDRONEPHROSIS

HOWARD G. HANLEY
M.D. Lpool, F.R.C.S.

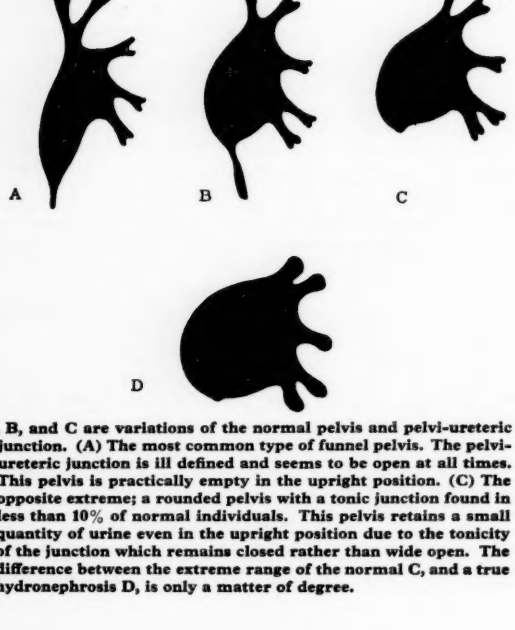
SURGEON, ST. PETER'S, ST. PAUL'S AND ST. PHILIP'S HOSPITALS, LONDON, W.C.2; UROLOGIST, ROYAL MASONIC HOSPITAL, LONDON, W.6, HILLINGDON HOSPITAL, MIDDLESEX; CONSULTING UROLOGIST, QUEEN ALEXANDRA'S MILITARY HOSPITAL, LONDON, S.W.1

RENAL surgery is becoming increasingly conservative, and most urologists today consider that a nephrectomy, though all too often necessary, is nevertheless an admission of failure. This view has been greatly sustained by such factors as earlier and more accurate diagnosis, improving anæsthesia, and the more effective control of urinary infection. This conservative trend is particularly well demonstrated in the approach to hydronephrosis due to disease at the pelvi-ureteric junction. Not many years ago "nephrectomy for pyonephrosis" was relatively common on any major operating-list, while a "conservative operation for hydronephrosis" was distinctly rare.

In contrast, the St. Peter's and St. Paul's Hospital report for 1958 records only 6 cases of pyonephrosis (4 nephrectomies) but there were 54 cases of hydronephrosis, only 12 of which were submitted to nephrectomy. Therefore, not only are hydronephrotic kidneys being detected earlier before they have become frank pyonephroses, but even the infected hydronephroses may now be amenable to conservative surgery, so that the only indication for nephrectomy in such cases is the almost complete absence of any useful renal parenchyma.

The ætiology of hydronephrosis has aroused controversy since the condition was first recognised, and many and varied theories have been put forward, but while it is probable that no single factor is responsible in all cases, it is equally certain that even the most obvious bands and vessels found at operation are not the initial cause of the pelvic dilatation, though they may be the factor which makes the obstruction irreversible, thus producing symptoms which lead to a diagnosis.

The fact that well over thirty authors have given their names to special types of plastic procedures (many of which are merely modifications or combinations of predecessors) indicates that the ideal operation has not yet been discovered, but a study of the ætiology makes it obvious that no one operation will ever suffice to effect a cure when there are a variety of causes. It seems that future progress in preserving hydronephrotic kidneys depends more upon a careful study of the causes than upon the devising of new surgical techniques, and it is relevant to consider the various new physiological conceptions concerning the conduction of urine from the renal tubules to the bladder.




**A, B, and C are variations of the normal pelvis and pelvi-ureteric junction. (A) The most common type of funnel pelvis. The pelvi-ureteric junction is ill defined and seems to be open at all times. This pelvis is practically empty in the upright position. (C) The opposite extreme; a rounded pelvis with a tonic junction found in less than 10% of normal individuals. This pelvis retains a small quantity of urine even in the upright position due to the tonicity of the junction which remains closed rather than wide open. The difference between the extreme range of the normal C, and a true hydronephrosis D, is only a matter of degree.**

### Emptying Mechanism of the Renal Pelvis

The theory that there is a set rhythm of conduction from calyces to pelvis to ureter to bladder is not borne out by hydrostatic or electrical experimentation (Trattner 1935, Lapides 1948, Hanley 1953), while actual visual observations using the X-ray image intensifier show that the pattern of conduction varies considerably, not only from one individual to another, but from minute to minute in the same kidney (Hanley 1955). Each particular segment of the system, be it calyx, pelvis, or ureter, reacts to the presence of fluid in a characteristic manner, the only stimulus to contraction being the presence of fluid in the lumen so that the movement pattern will obviously vary with the volume of urine excreted.

The pressure gradients from one segment to the next are extremely low (a few centimetres of water only) with the result that gravity plays a very important part in the normal emptying mechanism from the renal pelvis. For example if we try to perform excretion pyelography with the patient in the standing position there will be insufficient contrast medium in the pelvis to give any useful information in most cases. In fact the renal pelves are practically empty at all times in most people when they are standing up. The very low pressure differentials can explain many of the otherwise anomalous changes seen during the radiological study of the tract, especially under the X-ray intensifier.

A mild transitory cysto-urethritis will increase the tone or œdema of the uretero-vesical orifice and may cause slightly delayed emptying of the whole ureter, although it will be impossible to detect any "obstruction" with a ureteric catheter. In the same way the renal pelvis may distend quite considerably with only minor changes in hydrostatic pressure, while the calyces are continually altering their size and shape, not only because of their own muscular force, but because of the regurgitation of fluid from the contracting pelvis (Hanley 1959).

The importance of these observations lies in the fact that the pelvic size and shape can be easily altered in some people by changes of posture and urine volume, both of which are physiological factors, quite apart from extrinsic pressures which can be regarded as pathological factors. The reason why some individuals are more susceptible to these changes than others may well be a simple variation of the normal anatomy. A review of many thousands of routine pyelograms shows that very few renal pelves are alike in size or shape, or in their movement patterns, and that the "normal" covers a very wide range, extending from a funnel pelvis without any obvious pelvi-ureteric junction at one extreme, to a rounded pelvis with a well marked tonically closed junction at the other (see figure).

*The funnel pelvis* is by far the commonest type. It will empty completely in the standing position and is hardly affected at all even by extreme diuresis, any excess of fluid merely escaping through the wide-open junction into the upper ureter.

At the other extreme, the *rounded pelvis* has a tonically closed junction, and may retain small quantities of fluid even in the upright position. It is very sensitive to changes in urine volume and may enlarge quite considerably during periods of diuresis.

The upper ureteric segment just below the pelvis is rarely defined radiologically and contains urine only when the junction opens to discharge its contents.

These anatomical variations may well explain the development of a hydronephrosis in some instances. One would not expect a wide-open funnel pelvis to become hydronephrotic. On the other hand, a full rounded pelvis with a tonic junction may well become overdistended and turn into a true clinical hydronephrosis (fig. D). These assumptions have been confirmed during the surgical exploration of nearly 200 hydronephroses. When all the adhesions and bands and vessels had been cleared away, a smooth funnel junction which emptied freely and rapidly was found in less than 8% of the cases. The great majority showed a typical rounded pelvis with a clear-cut pelvi-ureteric junction and a relatively high insertion. Distension of the pelvis with saline produced active contractions, but these nearly always hesitated or stopped completely at the pelvi-ureteric junction and did not continue on smoothly into the upper ureter.

These clinical observations accord with Murnaghan's (1958) finding that there was an alteration in the arrangement of the muscle fibres at the junction in many hydronephroses, compared with the normal funnel-type pelves.

### Development of Hydronephrosis

It seems that true intrinsic strictures of the pelvi-ureteric junction are either congenital, in which case they produce a hydronephroses in childhood, or acquired due to inflammation or trauma, in which case they can cause trouble at any age. The youngest congenital example in this series was in a baby one day old, by which time the parenchyma was already destroyed.

Apart from children or adults with a long history of infection, however, a true mechanical narrowing of the lumen is very rare, and in the great majority of cases a bougie can be passed through the junction easily in both directions once the extrinsic adhesions have been freed. Unfortunately the fact that the lumen will admit a bougie does not necessarily mean that it will allow urine to pass freely, and this is a fundamental point in the ætiology of hydronephrosis. Even after the most meticulous ureterolysis, a majority of hydronephroses will be found to have this rounded full pelvis with a tonic junction which prevents the spontaneous escape of urine. Pelvic contractions may be very active but they stop short at the junction, and only an occasional wave passes on into the the ureter. Such a pelvis can certainly be made to empty easily by slight digital pressure, but it does not seem to be able to develop this slight increase in pressure by its own muscular contractions. For the purposes of treatment this is a vital observation, because having removed all vessels and bands from the region of the pelvi-ureteric junction we are still left with some anatomical factor as the primary cause of the distended pelvis, and this may well be a " tonic " junction.

*Intermittent Hydronephrosis*

The phenomenon of renal pain associated with an excessive diuresis is now becoming recognised by urologists as a definite clinical entity (Clarke 1959), and in this review we have encountered 6 proven examples of intermittent hydronephrosis. Excretion pyelograms performed on these patients after routine dehydration did not show any gross dilatation, but when the examination was repeated and they were given copious fluids to drink after the exposure of the five-minute film, a marked pelvic distension was seen within fifteen to thirty minutes. Without exception these pelves were of the rounded or full type with a tonic closed junction. It must be re-emphasised that in most cases this rounded pelvis with a tonic junction is perfectly consistent with normal renal function and is symptomless. The dividing line, however, between a rounded pelvis with a tonic junction and one with a hypertonic junction producing a true hydronephrosis is hard to define (see figure). Several of the patients with hydronephroses in this review gave a history indicating that they had had intermittent attacks of distension for a varying length of time—often for years—before the condition finally became irreversible.

Various factors may precipitate this final irreversible state, but it is easy to imagine that if a patient with intermittent dilatation of the pelvis also has awkwardly placed vessels or fibrous condensations of the fascia, the pelvi-ureteric junction could eventually prolapse through a vascular window, and once there it could not escape back again.

*Age-incidence*

Since this tonic junction is obviously present at birth it is interesting to speculate why a majority of " clinical " hydronephroses are not detected until adult life. Over half of the 180 conservative operations for hydronephrosis in this series were performed on young soldiers whose average age was 24, with a preponderance in the 18–19-year-old groups, and it is interesting to note that the average age of the civilian patients operated upon at St. Paul's or at Hillingdon Hospital was six years older than this (30 years). One possible explanation of this finding is that although both groups of patients had some potential cause for a hydronephrosis in their pelvi-ureteric junctions, some factor associated with military life drew attention to the fact earlier than would normally have been so. A very interesting feature in support of this theory was the large number of young soldiers who volunteered or admitted the information that their loin pain was precipitated or made worse by copious fluids, whereas this was not such a common finding in the older civilian group. There is certainly little doubt that many National Servicemen were subjected to strenuous exercise for the first time in their lives and therefore drank large volumes of fluid at irregular intervals; and some acquire a taste for beer.

### Diagnosis

The diagnosis of hydronephrosis can nearly always be made by excretion pyelography, and the phrase " non-functioning hydronephrosis " should be used with caution. In our experience " non-function " is a very unusual finding and there are very few hydronephroses which will not show some radiological shadow on a delayed film taken two to three hours after the injection of one of the newer " tri-iodine " contrast media. In fact, if a retrograde pyelogram is necessary to make the diagnosis, the kidney probably really is non-functioning and will have to be removed. A ureteric catheter must, however, always be passed immediately before operation to exclude disease of the bladder neck or ureter not revealed by the excretion pyelogram. In this series 3 mega-ureters, 1 ureteric calculus, and 2 primary carcinomas of the ureter (both under 25 years of age) were detected immediately before operation by this means.

*Retrograde Pyelography: a Warning*

The strongest warning should be given against the use of retrograde pyelography by the surgeon who is not prepared to carry on in the very near future (twenty-four hours at most) and perform a plastic procedure if neces-

sary. If there is even a remote chance that the patient will require transfer to another centre, or that operation will not be possible immediately, there is absolutely no justification for passing a ureteric catheter. It is not necessary for the diagnosis and may well destroy the kidney within a few hours. The danger is seldom due to the introduction of infection, but rather to the resultant overdistension which may prove the last straw and upset the equilibrium between urinary excretion, reabsorption, and escape through the junction. Even if the pelvis is carefully emptied by aspiration through the catheter after the X-ray is completed, the mere passage of the catheter will increase the œdema of the junction and may precipitate complete retention, in the same way that bladder retention can occur after catheterisation or cystoscopy in a man of prostatic age. We have seen 7 hydronephroses which were immeasurably damaged by a failure to observe this rule, and 2 were completely destroyed. One patient began to have rigors during a flight home from foreign parts, and a rapid nephrectomy revealed a widespread pyelonephritis with multiple abscesses throughout the parenchyma. The urine was known to have been sterile less than seventy-two hours previously.

## Surgery

*Indications*

Patients are often referred to the urologist with an excretion pyelogram showing a full rounded pelvis on one or perhaps both sides, and it is sometimes difficult to convince the patient and his doctors that the condition is within normal limits, and that "back pains" are infinitely more common than hydronephroses. Certain data are necessary, however, before one can say with reasonable certainty that a full rounded pelvis has not progressed beyond the limits of the normal range, and the emptying efficiency rather than the emptying rate is the most important single factor. A pelvis which is still shown as "filled" at the end of an hour in a dehydrated patient is not necessarily pathological unless it fails to empty in the upright position. It may simply be a "rounded pelvis with a tonic junction". If the contrast medium is not rapidly washed out by diuresis, and certainly if the pelvis increases greatly in size, it is most probably pathological.

As a general rule, by the time a hydronephrosis has produced sufficient symptoms to draw attention to itself, it has reached an irreversible and therefore a progressive state and should be treated by conservative surgery. The full rounded pelvis which is only moderately distended, however, presents the most difficult choice. In the absence of symptoms or where the discomfort is only of very recent onset, one should be patient and review the case in a few months' time. On the other hand, a long history of loin pain or of repeated short attacks, particularly if they are precipitated by a large fluid intake, should call for surgery. Such symptoms become worse not better, and the disease progresses steadily.

The long-term review of this series indicates that it is well worth trying to preserve the great majority of hydronephroses in young adults, and that any surgical exploration should be designed for conservative surgery rather than for nephrectomy.

In spite of the radiological appearances, and of the results of elaborate renal-function tests, the most important point in prognosis is the thickness of the renal parenchyma found at operation, and this may be quite unrelated to the size of the sac.

*Choice of Operation*

The series consists of well over 200 cases of hydronephrosis, 181 of which have been treated by conservative surgery. A Davis (1943) intubation type of operation was performed 69 times. The size of this group is due to the inclusion of many of the early cases where a splint was left in situ after a simple ureterolysis or a resection of the pelvis to avoid obstructing vessels, but where a true plastic operation at the junction was deemed unnecessary because there was no true intrinsic stricture. I would now perform a Foley (1937) or Culp (1951) on every "tonic" junction. The next largest group were those patients who had some form of incision through the junction followed by a flap closure (Foley 34, Culp 32). A simple ureterolysis without opening the pelvis was performed 10 times, and was combined with a pedicle sympathectomy on 8 occasions. There were 3 Hamilton-Stewart (1947) and 4 Priestley (1939) operations. The common factor in these 153 operations was the maintenance of anatomical continuity between pelvis and ureter.

The remaining 29 cases were treated by some form of operation which resected the pelvi-ureteric junction and joined the ureter to the pelvis at its most dependent point: Anderson and Hynes (1949) 16, von Lichtenburg (1929) 6, Kuster (1892) 4, Lubash and Madrid (1937) 3.

The introduction of the X-ray image intensifier (Hanley 1959) has been of inestimable value to us in the study of hydronephrosis, not only before operation as a guide to prognosis but also postoperatively when the functional results of different types of plastic procedures have been compared and studied in conjunction with the anatomy encountered. In general, the long-term results after operations where continuity between pelvis and ureter was preserved have been infinitely better than those in which complete resection and re-anastomosis was carried out. As observed on the intensifier screen the best emptying movements were seen after the Foley or Culp operations, and these have now become our operations of choice.

Nevertheless the intubated ureterostomy operations (Davis) have been clinically satisfactory, especially since they have been used in many of the most difficult cases, such as those with tight junctions associated with intrarenal pelves, and in 11 cases operated on for the second time. Although the newly formed segment tends to behave as a rigid tube when viewed under the intensifier, drainage is adequate and not one secondary nephrectomy has been necessary. This may not be such an æsthetic operation to perform, but it is a simple and safe procedure and is invaluable when in difficulties.

The type of operation performed, however, is probably of no great importance provided that there is an oblique (not a circular) scar, and that a "tonic junction" is converted into a wide-open "funnel junction" opening into normal ureter, by any technique preferred by the surgeon concerned. In principle, if a careful ureterolysis reveals a wide-open funnel junction over which waves pass smoothly into the ureter (and this is a rare finding), there will be no need for a plastic operation on the junction, although the pelvis may require resecting to overcome a high insertion or awkwardly placed vessels. When a tonic junction is found, as it will be in most cases, some form of refashioning to convert it into a funnel will be necessary if consistently satisfactory results are to be achieved.

*Long-term Results*

16 patients underwent successful bilateral operations, 11 were operated upon with success for a second, or even

a third time, and 9 women subsequently had 1 or more children without any urological complications.

No case of hypertension developing after a plastic operation has been recorded, though several patients experienced a slight but temporary drop in blood-pressure after operation.

Just over 72% of the 181 plastic operations have been traced. The most comprehensive review has been possible in the Service personnel, where "ability to serve" can be assessed much more objectively than merely asking the patient how he feels.

It is most encouraging to note that less than 12% of the men (including 6 with bilateral disease) were discharged on medical grounds, the remainder being able to complete their National, short, or full-time Service. 21 men are at present still serving, 16 of them in category P2 (FE) and five as P5.

A follow-up of those who have since left the Army shows that 4 of them subsequently had a nephrectomy performed elsewhere. An analysis of these 4 is instructive. 2 had pain and urinary infection, but the other 2 were symptom-free and uninfected though they still had radiological evidence of a dilated pelvis. It is doubtful whether nephrectomy was necessary. This last point emphasises the fact that success after a conservative operation for hydronephrosis is not measured by radiological changes in the pelvic outline, though improvement in this respect is always gratifying.

Success consists of (*a*) relief of pain, (*b*) relief of infection, and (*c*) arrest of the progress of the condition.

The most important point to emerge from this series dating back over twenty years is that in spite of the pessimistic outlook of many surgeons, conservative surgery is nearly always well worth while and that relatively few hydronephroses really require removing.

I wish to thank the Director-General, Army Medical Services, Lieut.-General Sir Alexander Drummond, for his kind permission to include the Service cases in this review, and also Colonel A. G. D. Whyte, reader in surgery at the R.A.M.C. College, for his great help in tracing the patients.

REFERENCES

Anderson, J. C., Hynes, W. (1949) *Brit. J. Urol.* **21**, 209.
Clarke, S. H. E. (1959) *ibid.* **31**, 396.
Culp, O. S., de Weerd, J. H. (1951) *Proc. Mayo. Clin.* **26**, 483.
Davis, D. M. (1943) *Surg. Gynec. Obstet.* **76**, 513.
Foley, F. E. B. (1937) *J. Urol.* **38**, 643.
Hanley, H. G. (1953) *Brit. J. Urol.* **25**, 358.
— (1955) *Brit. med. J.* ii, 22.
— (1959) *Brit. J. Urol.* **31**, 377.
Kuster, E. (1892) *Arch. klin. Chir.* **44**, 850.
Lapides, J. (1948) *J. Urol.* **59**, 501.
Lichtenberg, A. von (1929) *Amer. J. Surg.* **7**, 747.
Lubash, S., Madrid, A. (1937) *J. Urol.* **38**, 634.
Murnaghan, G. F. (1958) *Ann. R. Coll. Surg. Engl.* **23**, 25.
Priestley, J. T. (1939) *Surg. Gynec. Obstet.* **68**, 832.
Stewart, H. H. (1947) *Brit. J. Surg.* **35**, 51.
Trattner, H. R. (1935) *Urol. Cutan. Rev.* **39**, 81.

"... Where the scientist begins to head for confusion is when, like Humpty Dumpty, he takes perfectly ordinary words and tries to make them mean not what he has been taught at school they *do* mean but what he *wants* them to mean ... The physicist says 'hot', not when he means hot but when he means radio-active; and he is aggrieved at not being understood. Soon, by imperceptible steps, the stage is reached when one kind of scientist uses a word to mean one thing and another kind of scientist uses the same word to mean something quite different. For example, to a biologist 'plasma' is the liquid in which the blood corpuscles are suspended; but to a physicist 'plasma' is electrified gas. And so the different kinds of scientists grow away from each other just like prehistoric tribes which once shared the same grunts and clicks but which, as the areas they occupy separate, do so no longer."—MAGNUS PYKE. *Listener*, Sept. 8, 1960, p. 380.

# ATHEROSCLEROSIS AND BETA-GLUCURONIDASE

SEFIK KAYAHAN
M.D. Istanbul
*From the Department of Pharmacology and Therapeutics, University of Istanbul, Turkey*

ATHEROSCLEROSIS is a disease caused by metabolic changes. Disorders of lipid metabolism have been especially incriminated.

The thyroid (Dauber et al. 1949) and œstrogenic (Pick et al. 1951) hormones, which have been shown to lower the high plasma-cholesterol levels associated with atherosclerosis, are known to increase the β-glucuronidase activity (Fishman and Fishman 1944, Fishman et al. 1950, Pittoni and Barbieri 1953). Similarly heparin, used to lower the plasma-cholesterol level, also raises the serum-β-glucuronidase activity (Kayahan and Demiroglu 1959). The serum-β-glucuronidase activity of animals which are unsuitable for studying experimental atherosclerosis is much higher than that of those which are suitable for this purpose. For example, as a mean value, the serum-β-glucuronidase activity of cats is 10,000 units per 100 ml., of chickens 1820, of rabbits 1850 (Kayahan and Akçasu 1959). For these reasons, the role of β-glucuronidase in the pathogenesis of athersclerosis has been investigated.

## Animal Experiments

40 two-week-old chickens were studied.

These chickens were divided into four groups of 10. The first group was fed with commercial chicken mash. The second and third groups were both given commercial mash with 2% cholesterol and 5% cotton-seed oil for ten weeks, and the third group was also given 500 units daily β-glucuronidase by injection. The fourth group had the same diet as the second and third groups for six weeks, and then, in addition, β-glucuronidase 800 units was injected daily for four more weeks. At the end of ten weeks all the chickens were killed, and the β-glucuronidase activity, total-lipid, and total-cholesterol of their serum were estimated. In addition, the aortas were removed and examined for atherosclerotic lesions. To evaluate the aortic lesions quantitatively, the grading method of Horlick and Katz (1949) was used. The β-glucuronidase activity of the serum was determined by the method of Talalay et al. (1946).

TABLE I—THE EFFECT OF β-GLUCURONIDASE IN CHOLESTEROL-FED CHICKENS

| Experimental groups | Degree of aortic atherosclerosis | Serum-total-lipid (mg. per 100 ml.) | Serum-cholesterol (mg. per 100 ml.) | Serum-β-glucuronidase activity (units per 100 ml.) |
|---|---|---|---|---|
| 1 | 0 | 242–386 (*306*) | 90–115 (*102*) | 1230–2880 (*1820*) |
| 2 | 0·7–2·8* (*2·1*) | 3238–6226 (*4854*) | 850–1420 (*1185*) | 750–1420 (*890*) |
| 3 | 0–1 (*0·1*) | 722–986 (*824*) | 420–685 (*575*) | 1340–3250 (*2320*) |
| 4 | 0·2–1·2 (*0·5*) | 1326–2435 (*1862*) | 660–930 (*785*) | 1290–3120 (*2130*) |

* The figures give the range of values; the averages are in parentheses.

### *Results*

The effect of β-glucuronidase on cholesterolæmia, lipæmia, serum-β-glucuronidase levels, and aortic atherosclerosis is shown in table I.

### *Conclusions*

Feeding with cholesterol decreased the serum-β-glucuronidase activity in the second group of chickens. The severity and grade of aortic atherosclerosis were lower in the third and fourth groups than in the second group. The serum-cholesterol levels of the third and fourth groups did not rise as much as those of the second

group. The serum-β-glucuronidase activity was increased when this enzyme was administered.

These findings suggest that β-glucuronidase has a preventive and probably a therapeutic effect on experimental atherosclerosis.

### Observations on Patients with Atherosclerosis

Three different investigations were made:

1. The β-glucuronidase activity of the serum was estimated in 20 normal and 20 atherosclerotic patients.

2. The β-glucuronidase activity of the intima was determined in 10 normal and 10 atherosclerotic human aortas. The intima of the normal aorta and of the atherosclerotic lession was dissected, and the enzyme activity per gramme of tissue was estimated in the homogenate prepared from them.

3. The effect of β-glucuronidase on the serum-lipids and on the clinical manifestations of atherosclerosis was studied in 10 atherosclerotic patients. β-glucuronidase 25,000 units daily was injected intramuscularly for fifteen days, and after that the same amount was given weekly for two more weeks.

The patients chosen for the third study were:

CASE 1.—A man of 48, with retrosternal pain on exertion for three years.

CASE 2.—A man of 50 with precordial pain on exertion for three months, and an anterior myocardial infarction ten days before admission to the clinic, was treated only with β-glucuronidase.

CASE 3.—A woman, aged 58, with intermittent claudication in her left leg for two years, and retrosternal pain on exertion for three years. About six weeks before admission to hospital a small ulcer appeared on her left 5th toe. The dorsalis pedis, posterior tibial, and polpiteal arteries were not palpable on the left.

CASE 4.—A 60-year-old man, with mild diabetes for fifteen years, and retrosternal pain on exertion for three years.

CASE 5.—A man of 63, with a duodenal ulcer and precordial pain on exertion for three years.

CASE 6.—A 63-year-old man, with mild diabetes for nine years, and retrosternal pain on exertion for eight years.

CASE 7.—A man, aged 65, with retrosternal pain on exertion for six years.

CASE 8.—A man of 68, with precordial pain on exertion for four years.

CASE 9.—A 70-year-old man, with intermittent claudication in his right leg for three years, and retrosternal pain on exertion and at rest for six months. Four months previously he had had a posterior myocardial infarction. A small patch of gangrene developed on his right 5th toe a month before admission to the clinic. The dorsalis pedis, posterior tibial, and popliteal arteries were not palpable on the right. The minute blood-volume, measured by plethysmography, was 0·1 ml. in this foot (normal value 4–6 ml.).

CASE 10.—A man of 85, with mild diabetes for eighteen years, and retrosternal pain on exertion and intermittent claudication in both legs for two years. The dorsalis pedis, posterior tibial, and popliteal arteries were not palpable on either side. The minute blood-volume was 0·6 ml. in each foot. In all these cases, electrocardiograms taken at rest showed positive signs of coronary insufficiency.

I studied the effect of β-glucuronidase on total lipæmia, total cholesterolæmia, coagulability of the blood, electrocardiographic signs, electrophoretic properties of the serum-lipids, serum-β-glucuronidase level, and on their symptoms.

The β-glucuronidase activity was estimated as before.

α and β lipoproteins of the serum were examined by paper electrophoresis, using Whatman no. 31 paper and barbitone sodium buffer at pH 8·6; the paper was stained with Sudan black, and the β/α lipoprotein ratio was calculated.

The coagulability of the blood was determined by the heparin-tolerance test. Oxalated blood from the patient and from a normal subject was centrifuged to separate the plasma. After recalcification of the plasma 1 unit of heparin was added to 0·5 ml. of this plasma, and then the coagulation-time was measured. From these values the following index was calculated:

$$\frac{\text{Heparin tolerance of patient}}{\text{Heparin tolerance of normal subject}} \times 100 = \text{Index}$$

A value lower than 100 indicates hypercoagulability, and higher than 100 indicates hypocoagulability (Kaulla 1953).

TABLE II—β-GLUCURONIDASE ACTIVITY OF THE SERUM AND INTIMA

| Subjects | Serum-β-glucuronidase activity (units per 100 ml.) | Aortas | β-glucuronidase activity of aortic intima (units per g.) |
|---|---|---|---|
| 20 normal cases | 750–1250 (Average *980*) | 10 normal intimas | 12·9–16·6 (average *14·2*) |
| 20 atherosclerotic patients | 360–830 (average *620*) | 10 atherosclerotic intimas | 0–5·7 (average *2·3*) |

*Results*

The results of the first and second investigations are shown in table II, and those of the third investigation in table III.

*Conclusion*

The finding that β-glucuronidase activity in the serum of atherosclerotic patients and in atherosclerotic intimas is lower than that found in normals suggests a correlation between atherogenesis and β-glucuronidase. Under the influence of β-glucuronidase the total lipæmia, the total cholesterolæmia, and the lipid bound to β-globulin all decreased, while the lipid bound to α-globulin and the serum-β-glucuronidase activity increased in every patient.

TABLE III—EFFECT OF β-GLUCURONIDASE ON SERUM-LIPIDS, SERUM-β-GLUCURONIDASE ACTIVITY, AND BLOOD COAGULABILITY

| Cases | Serum-β-glucuronidase activity (units per 100 ml.) | | Total lipæmia (mg. per 100 ml.) | | Total cholesterolæmia (mg. per 100 ml.) | | β/α lipoprotein | | Coagulability index | |
|---|---|---|---|---|---|---|---|---|---|---|
| | B* | A† | B | A | B | A | B | A | B | A |
| 1 | 360 | 420 | 969 | 593 | 310 | 175 | 7·8 | 5·14 | 66 | 108 |
| 2 | 474 | 574 | 1250 | 625 | 270 | 150 | 12 | 6·44 | 62 | 107 |
| 3 | 462 | 528 | 1218 | 781 | 330 | 200 | 7·3 | 4·28 | 72 | 115 |
| 4 | 378 | 515 | 1500 | 860 | 360 | 220 | 13·1 | 8·15 | 60 | 113 |
| 5 | 586 | 682 | 906 | 750 | 240 | 200 | 9·14 | 6·87 | 74 | 117 |
| 6 | 715 | 825 | 1247 | 920 | 285 | 200 | 11·5 | 7·49 | 59 | 106 |
| 7 | 826 | 848 | 1285 | 758 | 325 | 175 | 12·3 | 6·47 | 64 | 122 |
| 8 | 472 | 508 | 1382 | 768 | 345 | 185 | 10·9 | 7·12 | 67 | 109 |
| 9 | 386 | 415 | 912 | 656 | 220 | 165 | 8·64 | 4·78 | 63 | 118 |
| 10 | 524 | 562 | 750 | 652 | 250 | 150 | 9·82 | 5·47 | 68 | 111 |

* B = before treatment. † A = after treatment.

The heparin tolerance test revealed hypercoagulability of the blood in these patients at first, but with β-glucuronidase treatment the blood became hypocoagulable.

All 10 patients improved clinically. The precordial pain on exertion disappeared in the first 8 cases, and the electrocardiograms in 5 cases returned to normal. The necrosis of the toes in cases 3 and 9 completely healed in twenty days, and the walking capacity of cases 3, 9, and 10 had increased considerably at the end of treatment. In cases 9 and 10 the minute blood-volume of the foot was only very slightly raised, and the arterial pulsations of the legs did not change, but the rapid healing suggests that β-glucuronidase increased the cell proliferation and tissue regeneration.

### Discussion

Levvy et al. (1948) suggested the role of β-glucuronidase in tissue regeneration, and its topical application has cured diabetic and varicose ulceration very quickly (Kayahan 1959). This also shows that β-glucuronidase promotes tissue regeneration and protein synthesis.

The present results suggest that β-glucuronidase is an enzyme which has a profound effect on the metabolism of lipids and also on the metabolism of proteins—both of which contribute to the development of atherosclerosis when altered. Thus an enzyme defect—the defect of β-glucuronidase—may play a part in the pathogenesis of atherosclerosis, and β-glucuronidase may have a therapeutic effect.

I am grateful to Prof. Sedat Tavat, head of the department, for his interest and encouragement in this work.

REFERENCES

Dauber, D. V., Horlick, L., Katz, L. N. (1949) *Amer. Heart J.* **38**, 25.
Fishman, W. H., Fishman, L. W. (1944) *J. biol. Chem.* **152**, 487.
— Odell, L. D., Gill, J. E., Christensen, R. A. (1950) *Amer. J. Obstet. Gynec.* **59**, 414.
Horlick, K., Katz, L. N. (1949) *Amer. Heart J.* **38**, 336.
Kaulla, K. N. (1953) *Dtsch. med. Wschr.* **78**, 1075.
Kayahan, S. (1959) Unpublished data.
— Akçasu, A. (1959) Unpublished data.
— Demiroglu, C. (1959) Unpublished data.
Levvy, G. A., Kerr, L. M. H., Campbell, J. G. (1948) *Biochem. J.* **42**, 462.
Pick, R., Stamler, J., Rodbard, S., Katz, L. N. (1951) *Circulation*, **4**, 468.
Pittoni, A., Barbieri, E. (1953) *Boll. Soc. ital. Biol. sper.* **29**, 342.
Talalay, P., Fishman, W. H., Huggins, C. (1946) *J. biol. Chem.* **166**, 757

# BLOOD-VOLUME AND TOLERANCE TO PENTOLINIUM IN THE TREATMENT OF HYPERTENSION

VAGN RØNNOV-JESSEN
M.D. Copenhagen

ASSISTANT PHYSICIAN TO THE COPENHAGEN COUNTY HOSPITAL, MEDICAL DEPARTMENT F, GENTOFTE, DENMARK

WHEN bisquaternary ganglion-blocking agents are given in cases of arterial hypertension, tolerance to the drug will ordinarily develop in the course of days or weeks. This increasing tolerance is especially significant for hexamethonium and some other earlier compounds, such as pentamethonium and hexamethylene-bis-dimethylethyl ammonium bromide (Smirk 1952). With more recent drugs like pentolinium (' Ansolysen ') and mecamylamine (' Inversine ') tolerance will also increase, but to a lesser degree than with hexamethonium (Smirk 1953, 1957, Freis et al. 1954).

Retention of salt and water during treatment with hexamethonium or pentolinium has been described (Fraser and Lowe 1954, Rønnov-Jessen 1954, 1955). This is sometimes followed by a considerable fall in the hæmoglobin level, which corresponds to an increase of the blood-volume. In 1954 I observed in some cases an increase in tolerance to pentolinium together with salt and water retention. When the surplus salt was excreted, the original tolerance was re-established. But the possibility that the increase of tolerance is due to retention of salt and water was not confirmed in a bigger series of patients.

For many years it has been known that a diet poor in salt enhances the hypotensive effect of ganglion-blocking compounds (Smirk and Alstad 1951, Smirk 1953, Freis et al. 1954). The same effect has been observed with mercurial diuretics.

Recently many observations on the potentiating effect of chlorothiazide on ganglion-blocking agents have been reported. Tapia et al. (1957), Freis et al. (1958), Dustan et al. (1959), and Dollery et al. (1959) all found that when hypertensive patients were treated with chlorothiazide the plasma-volume decreased, and they assumed that this is the most important reason for the decrease of tolerance for ganglion-blocking compounds. Dollery et al. have proved that the sensitivity to pentolinium will decrease again when the diminished blood-volume is corrected with dextran devoid of salt.

These findings conform with the experience of Freis et al. (1951), who found that in hypertensive patients treated with hexamethonium even a small quantity—i.e., a few hundred millilitres—of blood removed by venesection often caused a significant fall in blood-pressure. This fall was promptly counteracted by reinfusion of the blood.

The changes in sensitivity during treatment with pentolinium seem to be mostly due to variations in the blood-volume.

## The Study

Eight ambulant patients were studied, all with severe fixed hypertension but without uncompensated heart-disease. During the study the patients had a low-salt diet, but they were given additional salt—sodium chloride 4 g. daily—to ensure a constant salt intake (a total of 5–5·5 g. sodium chloride daily).

The patients were first given pentolinium alone for a few days, and then both pentolinium and a drug of the chlorothiazide group. We measured repeatedly the blood-volume of the patients, and their concurrent sensitivity to pentolinium, before and during the drug trials.

*Blood-volume*

Blood-volume was determined by means of hexavalent radioactive sodium chromate ($^{51}Cr$). The red blood-cells of the patients were marked in vitro, and washed twice in physiological sodium chloride. The marked erythrocytes were injected intravenously as a 20 ml. suspension of physiological sodium chloride after samples have been taken for standard comparison. 15–20 minutes later venous blood was taken without stasis, using dried heparin as an anticoagulant. Hæmolysis was produced by cooling below 20°C, and the activities of standard and hæmolysed blood samples were measured in a well-type scintillation counter.

The blood-volume itself was calculated as the ratio between injected activity and activity per millilitre of blood. If another determination of blood-volume was made before the activity of the first injection had disappeared, the volume was worked out from the ratio between the last injection of active suspension and the increase of activity per millilitre of blood. The calculation was always tested twice, and counting was continued until the statistical error was less than 2%.

The reliability of this method was checked by making two blood-volume determinations on each of ten patients within 45 minutes. The difference between the two varied from 1·2 to 6·3%, with an average of 3·7%.

*Sensitivity to Pentolinium*

Variations in the sensitivity to pentolinium were shown by giving the same test dose of the drug intravenously before, and several times during, the treatment. The test doses, injected at least 12 hours after the previous dose of pentolinium, ranged from 1 to 3·5 mg. of pentolinium bitartrate.

Before the injection the blood-pressure was measured with the patient erect and lying down every 2nd minute until three consecutive results were constant. After the injection

TABLE I—BLOOD-VOLUME AND WEIGHT BEFORE AND AFTER 3–8 DAYS' TREATMENT WITH PENTOLINIUM

| Case no. | Date | Blood-volume (ml.) | | Difference (%) | Weight (kg.) | | Difference (%) |
|---|---|---|---|---|---|---|---|
| | | Before | After | | Before | After | |
| 1 | Sept. 22 „ 26 | 2750 | 3280 | +19·3 | 37·7 | 39·0 | +3·4 |
| 2 | Aug. 28 Sept. 1 | 5150 | 5340 | + 3·9 | 80·3 | 80·1 | −0·2 |
| 3 | July 21 „ 27 | 3610 | 3760 | + 4·2 | 67·3 | 68·5 | +1·8 |
| 4 | Dec. 16 „ 20 | 3500 | 3770 | + 7·7 | 82·8 | 83·1 | +0·4 |
| 5 | Oct. 14 „ 19 | 4790 | 4320 | − 9·8 | 72·8 | 72·2 | −0·8 |
| 6 | Feb. 16 „ 24 | 4130 | 3930 | − 4·8 | 73·6 | 73·1 | −0·7 |
| 7 | Nov. 18 „ 21 | 4470 | 4940 | +10·4 | 85·2 | 85·6 | +0·5 |
| 8 | Oct. 23 „ 28 | 4490 | 4550 | + 1·3 | 83·1 | 82·4 | −0·8 |

TABLE II—RELATION BETWEEN BLOOD-VOLUME AND SENSITIVITY TO PENTOLINIUM

| Case no. | — | Before treatment | During treatment with pentolinium | After 3–9 days' treatment with pentolinium and chlorothiazide or hydrochlorothiazide | After blood-volume was corrected with 6% salt-free dextran |
|---|---|---|---|---|---|
| 1 | Blood-volume (ml.)<br>Reduction in M.B.P.* | 2750<br>17 | 3280<br>10 | 2830<br>21 | ..<br>.. |
| 2 | Blood-volume (ml.)<br>Reduction in M.B.P. | 5150<br>17 | 5340<br>6 | 4670<br>22 | ..<br>.. |
| 3 | Blood-volume (ml.)<br>Reduction in M.B.P. | 3610<br>40 | 3760<br>30 | 3220<br>48 | 3700<br>31 |
| 4 | Blood-volume (ml.)<br>Reduction in M.B.P. | 3500<br>40 | 3770<br>31 | 3120<br>?† | 3610<br>42 |
| 5 | Blood-volume (ml.)<br>Reduction in M.B.P. | 4790<br>32 | 4320<br>56 | 4140<br>50‡ | ..<br>.. |
| 6 | Blood-volume (ml.)<br>Reduction in M.B.P. | 4130<br>29 | 3930<br>32 | 3750<br>56 | ..<br>.. |

* M.B.P. = mean blood-pressure (mm. Hg) in the erect position.
† During hydrochlorothiazide therapy the blood-pressure decreased so much that it was impossible to complete the sensitivity test.
‡ Because of the greatly increased sensitivity to pentolinium the third test dose was reduced to two-thirds of the previous ones.

the blood-pressure was measured every 3–5 minutes for half an hour (8 times) with the patient in the same positions as before. The greatest fall in the mean blood-pressure in the erect position was used as a measure for sensitivity to pentolinium. The fall of blood-pressure when the patient was lying down was too inconstant for one to draw any conclusions about variations in sensitivity.

The mean blood-pressure was calculated from the diastolic pressure plus a third of the pulse pressure. The measurements were made with a standard mercury sphygmomanometer.

## Results

Table I shows the variations in blood-volume and body-weight during pentolinium treatment. The blood-volume of six patients increased while that of two decreased. The body-weight variations were negligible.

Tables II and III show the relation between blood-volume and sensitivity to pentolinium in the eight patients at different stages of treatment. In the six with increasing blood-volumes the sensitivity decreased (cases 1–4, 7, and 8). In the two with decreasing blood-volumes the sensitivity to pentolinium increased (cases 5 and 6). In two patients (cases 7 and 8) the volume again fell during continued pentolinium treatment, and at the same time the sensitivity to the drug increased.

In six cases the investigations were resumed after some days of combined treatment with pentolinium and chlorothiazide or hydrochlorothiazide. In five the blood-volume decreased and the sensitivity to pentolinium increased, in one case so much that the test dose of pentolinium had to be reduced by one-third (case 5). In the last patient (case 4) the decrease of blood-volume was also significant; at the same time her blood-pressure became almost normal in the erect position, and a test dose of pentolinium was not given.

Both in this patient and in another (cases 3 and 4) the sensitivity was tested after correction of the reduced blood-volume to about the original level by infusion of a 6% salt-free solution of dextran. The sensitivity was almost the same as before treatment was begun.

In two patients (table III) the investigations were repeated after about $2^1/_2$ months' treatment with hydrochlorothiazide and pentolinium. In case 7 the blood-volume at the last measurement was nearly the same as before treatment, while the sensitivity to pentolinium had increased. In case 8 the blood-volume increased by about 3% while the sensitivity was almost unchanged.

TABLE III—RELATION BETWEEN BLOOD-VOLUME AND SENSITIVITY TO PENTOLINIUM

| Case no. | — | Before treatment | During treatment with pentolinium | | During prolonged combined treatment with pentolinium and hydrochlorothiazide |
|---|---|---|---|---|---|
| 7 | Blood-volume (ml.)<br>Reduction in M.B.P. | 4470<br>35 | After 3 days:<br>4940<br>19 | After 13 days:<br>4680<br>34 | After 72 days:<br>4450<br>42 |
| 8 | Blood-volume (ml.)<br>Reduction in M.B.P. | 4490<br>43 | After 5 days:<br>4550<br>41 | After 11 days:<br>4260<br>48 | After 81 days:<br>4630<br>46 |

## Discussion

The relation between blood-volume and sensitivity to pentolinium in this study indicates that the initial increase in tolerance for pentolinium and the increased sensitivity when chlorothiazide is given concurrently are due respectively to an increase and decrease in blood-volume. An increasing tolerance has only been seen when the blood-volume has increased at the same time.

This study shows, like those of Dollery et al. (1959), that when the blood-volume, reduced by treatment with chlorothiazide, is restored by means of dextran devoid of salt, the sensitivity to pentolinium falls to the original level. This indicates that the increased sensitivity to pentolinium during treatment with chlorothiazide is almost entirely due to reduction of blood-volume and not to reduction of salt and water—and this is always so if the treatment with chlorothiazide lasts for a few days only. At the same time the assumption that chlorothiazide has a specific anti-hypertensive effect is disproved.

On the other hand Wilkins et al. (1958) and Wilson and Freis (1959) have found that during prolonged therapy with chlorothiazide the blood-volume and the extracellular fluid will, in the course of a few months, return to normal without the blood-pressure increasing as much as before. One cannot therefore exclude a specific hypotensive effect of chlorothiazide during long-continued treatment.

As shown in the tables the sensitivity changes in some cases are greater than can be explained from the changes in blood-volume; but they are not greater than can be expected when the inaccuracies of determining the blood-volumes and blood-pressures are taken into consideration.

We do not fully understand the relation between the blood-volume and sensitivity to pentolinium. Dustan et al. (1959) have shown, however, that during treatment of hypertension with chlorothiazide a compensatory increase in vasomotor tone will develop as in oligæmia from other causes, and maintain the hypertension. This provides a reasonable explanation of why the effects of ganglion-blocking agents are enhanced. Furthermore these workers found that after correcting the decreased blood-volume with dextran the peripheral resistance again declined—a sign of decrease in vasomotor tone following the increase of blood-volume.

If these results are tenable, a theoretical explanation of the initial increase of tolerance during treatment with pentolinium could be:

Because of the fall in blood-pressure following pentolinium

therapy the blood-volume will increase. When the blood-volume increases, the neurogenic component of blood-pressure regulation diminishes, and consequently the effect of pentolinium also decreases.

Hence this study suggests that the vasomotor ganglia themselves do not develop tolerance to pentolinium, but that the apparent increase of tolerance is conditioned by the increase in blood-volume.

This study also clarifies the relation between variations in blood-volume and the sensitivity of hypertensive patients to pentolinium only. If the above theoretical explanation is correct, the same mechanisms must contribute to the development of tolerance in treatment with any ganglion-blocking drug. If in addition tolerance to these drugs happened to develop in the vasomotor ganglia themselves, this could be investigated along the same lines as the ones followed in this study.

The relatively small changes in tolerance during treatment with the newer ganglion-blocking compounds are presumably based primarily on an increase of blood-volume, as in pentolinium therapy. Preliminary investigations suggest that this is so with the tertiary amine, pempidine tartrate. The very great increase of tolerance during treatment with hexamethonium has not yet been fully explained, but this increase also seems to be conditioned by an increase of blood-volume (Rønnov-Jessen, to be published).

### Conclusions

In treating hypertension with pentolinium there is usually some increase of blood-volume when the sensitivity to pentolinium decreases.

During continued therapy with pentolinium and chlorothiazide derivatives blood-volume again decreases and the sensitivity to pentolinium increases.

When the reduced blood-volume is corrected by means of dextran devoid of salt, the sensitivity to pentolinium will reach about the same stage as before treatment.

In two patients treated with pentolinium and hydrochlorothiazide for about $2^1/_2$ months, the sensitivity to pentolinium also depended on the blood-volume.

Thus when pentolinium is given the increase of tolerance is mainly due to an increase of blood-volume. As in earlier investigations, the increase of sensitivity during treatment with chlorothiazide is conditioned by a reduction of blood-volume.

The investigations of Dustan et al. (1959) suggest that the increase of sensitivity to ganglion-blocking agents caused by chlorothiazide depends on an increase of vasomotor tone concurrent with the reduction in blood-volume. It seems reasonable to presume, therefore, that during treatment with pentolinium the vasomotor tone declines when the blood-volume increases.

The present study shows that it is unlikely that the vasomotor ganglia themselves develop tolerance to pentolinium. The apparent increase of tolerance is conditioned by an increase in blood-volume, which probably causes a decrease of vasomotor tone.

May & Baker Ltd. supplied the pentolinium compounds.

#### REFERENCES

Dollery, C. T., Harington, M., Kaufmann, G. (1959) *Lancet*, **i**, 1215.
Dustan, H. P., Cumming, G. R., Corcoran, A. C., Page, I. H. (1959) *Circulation*, **19**, 360.
Fraser, J. R. E., Lowe, T. E. (1954) *Aust. Ann. Med.* **3**, 234.
Freis, E. D., Partenope, E. A., Lilienfield, L. S., Rose, J. C. (1954) *Circulation*, **9**, 540.
— Stanton, J. R., Finnerty, F. A., Schnaper, H. W., Johnson, R. L., Rath, C. E., Wilkins, R. W. (1951) *J. clin. Invest.* **30**, 435.
— Wanko, A., Wilson, I. M., Parrish, A. E. (1958) *J. Amer. med. Ass.* **166**, 137.

*References continued at foot of next column*

## ALLEVIATION OF POST-HERPETIC NEURALGIA

D. TAVERNER
M.B.E., M.D. Leeds. F.R.C.P.
READER IN MEDICINE, UNIVERSITY OF LEEDS

MOST patients recover from herpes zoster with no ill effects apart from scarring of the skin. A few—usually elderly—patients continue to have intractable and distressing pain in the affected area; in some of these cases the pain of the acute eruption persists unabated, while in others there is a free interval. This post-herpetic neuralgia may improve spontaneously, but usually it lasts throughout life and causes severe and constant distress, if not despair.

Although many treatments have been recommended, it is generally agreed that none is effective. Even extensive neurosurgical procedures are unlikely to give relief; leucotomy itself is often ineffective.

Russell and his colleagues (Russell et al. 1957, Russell 1959) have claimed good results from the repeated percussion of the affected area with an electric vibrator. This method was originally tried in some of my cases; but it was not helpful because the patients were so eager for relief that they soon began to injure their skin by injudicious percussion.

The mechanism of post-herpetic neuralgia is not understood, but it has been postulated that pain is experienced when abnormal patterns of nerve impulses reach the central nervous system (Gooddy 1957). In most cases there is evidence of defective innervation of the damaged skin, and it seemed reasonable to attempt to modify the pattern of nerve impulses travelling to the central nervous system by setting up fresh patterns. The satisfactory use of skin-cooling sprays for the treatment of pain from other causes (Travell and Rinzler 1952) led me to test this method in post-herpetic neuralgia. The results in 16 cases are reported here.

### Method

At first the skin over the painful area was sprayed continuously at a range of 24 in. with ethyl chloride for 30–60 seconds, taking care to move the spray slowly so that the skin did not freeze. It was later found that intermittent spraying for 5 seconds every half minute for 2 minutes was equally effective, and that much less skin damage resulted. When spraying the head it was only necessary to warn the patient to keep his eyes firmly closed. Application of silicone barrier cream or a prednisone spray relieved persistent redness and blistering of the skin even when spraying with ethyl chloride was continued.

Ethyl chloride, sprayed through a coarse nozzle, is very effective; but its use, especially by lay people, is attended by hazards due to its flammability, its general-anæsthetic activity, and the ease with which it may freeze and injure the skin.

It is essential to use a vigorous spray; and the ethyl-chloride spray, general-anæsthetic pack with long nozzle (Hedley, no. 13) is the most suitable of those commercially available. The local-anæsthetic pack, and the general-anæsthetic pack with short nozzle, give a very fine spray which is usually ineffective. In most patients the first few applications of the spray cause severe pain and even distress, but the subsequent relief soon

#### DR. RØNNOV-JESSEN: REFERENCES—*continued*

Rønnov-Jessen, V. (1954) *III Int. Congr. intern. Med., Stockh.* p. 157.
— (1955) *Lancet*, **i**, 122.
Smirk, F. H. (1952) *ibid.* ii, 1002.
— (1953) *ibid.* i, 457.
— (1957) High Arterial Pressure ; p. 592. Oxford.
— Alstad, K. S. (1951) *Brit. med. J.* i, 1217.
Tapia, F. A., Schneckloth, R. E., Dustan, H. P. (1957) *Clin. Res. Proc.* **5**, 293.
Wilkins, R. W., Hollander, W., Chobanian, A. V. (1958) *Ann. N.Y. Acad. Sci.* **71**, 465.
Wilson, I. M., Freis, E. D. (1959) *Circulation*, **20**, 1028.

DATA ON 16 CASES OF POST-HERPETIC NEURALGIA

| Case no. | Sex | Age (yr.) | Site | Duration (yr.) | Relief (mos) | Comment |
|---|---|---|---|---|---|---|
| *Failures:* | | | | | | |
| 1 | M | 76 | Lt trigem I | 13 | 0 | Alcohol injection gasserian ganglion |
| 2 | F | 66 | Rt T8–10 | 4 | 0 | Deep X-ray |
| 3 | F | 74 | Rt T7 | 9 | 0 | Dorsal rhizectomy |
| 4 | M | 64 | Rt trigem I | 1·5 | 0 | Itching only |
| *Successes:* | | | | | | |
| 5 | F | 67 | Lt trigem I | 1·1 | 6 | .. |
| 6 | F | 73 | Lt T11 | 4 | 12 | Relapsed on L.A.P.* |
| 7 | F | 72 | Rt occip | 0·9 | 8 | "Wonderfully better" |
| 8 | M | 65 | Rt trigem I, II | 2 | 18 | Needs repeated sprays |
| 9 | M | 82 | Rt trigem I | 5 | 15 | "A godsend" |
| 10 | F | 69 | Rt T12 | 2·5 | 21 | "A world of good" |
| 11 | M | 65 | Lt T9 | 2 | 3 | "Much better" |
| 12 | F | 59 | Rt T5–7 | 5 | 9 | Relapsed on L.A.P.* |
| 13 | M | 64 | Rt C4–7 | 6 | 3 | " |
| 14 | F | 72 | Rt trigem I | 2·5 | 3 | " |
| 15 | F | 86 | Rt C5 | 6 | 12 | .. |
| 16 | F | 76 | Rt T4 | 1 | 10 | .. |

* Local-anæsthetic pack.

makes the patient willing to undergo this initial temporary discomfort. At the beginning of treatment patients are sprayed daily by the doctor; but once the patients, or their relatives, are familiar with the technique, they are instructed to continue the treatment at home. It is best to try to "drive" the pain away by spraying whenever severe pain recurs. Sometimes remission takes place only after two or three sprayings, but thereafter steadily increasing periods of relief ensue.

*The Patients*

16 patients (6 men, 10 women) were studied (see accompanying table). Their ages ranged from 59 to 86 (mean 70·6) years. Post-herpetic neuralgia involved the trunk in 9 and the head in 7; the duration of the condition ranged from 10 months to 13 years (mean 4·1 years).

## Results

*Successes*

In 12 cases the pain was relieved satisfactorily. 2 of these are now in remission and do not use the spray at all. The others spray themselves or are sprayed by relatives whenever severe pain recurs; the intervals between spraying vary from daily to once or twice per week. All these patients are delighted with their treatment and describe it in terms such as "a godsend", "has done me a world of good", "wonderfully better", and "much better". Sometimes the gratitude of these people, relieved of the pain they had expected to persist indefinitely, has been embarrassing. The duration of relief has varied from 3 months to 21 months (mean 10·0 months).

4 patients were found, on review after an interval of some months, to have abandoned the use of the spray on the ground that it was no longer effective. In each case it was discovered that the patient had inadvertently been issued with a different kind of spray. This was a local-anæsthetic pack which has a much more feeble impact than the general-anæsthetic pack. When these 4 patients were supplied with the correct type of spray, further and persisting relief resulted. Another patient was referred by the private doctor because the spray treatment was ineffective. Here, too, it was found that the local-anæsthetic pack had been used; and on changing to the general-anæsthetic pack satisfactory relief was obtained.

*Failures*

4 patients failed to obtain satisfactory relief and the treatment was abandoned.

In 2 the neuralgia affected the head and in 2 the trunk. The duration of neuralgia in these 4 patients was 13, 9, 4, and 1·5 years. 1 patient had undergone dorsal rhizectomy 8 years before, 1 had undergone alcohol injection into the gasserian ganglion 7 years before, and 1 had received deep X-ray therapy to the spinal cord 4 years before; the 4th had not previously been treated.

The 3 previously treated patients showed little response to the spray and this method was eventually abandoned. No other form of treatment was found effective in these cases.

In the 4th case an initial period of satisfactory relief was followed by relapse which was thought to be due possibly to emotional tension between the patient and his wife. The spray was discontinued for some months, and when treatment was resumed by me satisfactory relief was not obtained. It seemed likely that pain had in fact been abolished, but the patient complained so bitterly of persistent itching that the result was regarded as unsatisfactory.

### Illustrative Case-records

**Case 5.**—A woman, aged 67, had had post-herpetic neuralgia for 13 months in the area of the first division of the left trigeminal nerve. This responded to mechanical vibration, but the skin was soon damaged. Initial treatment with ethyl chloride gave 9 hours' relief from pain. After once-daily spraying for a week relief for up to 72 hours or more was achieved. She then remained well for 6 months without therapy, but the pain recurred after a severe emotional shock. This was again relieved by the spray, and the patient has remained pain-free with occasional sprayings ever since.

**Case 9.**—A man, aged 82, had had post-herpetic neuralgia for 4 years, affecting the first division of the right trigeminal nerve. He was in a neurosurgical ward, and the neurosurgeon had just written: "The patient is complaining bitterly. I shall try gasserian ganglion injection of alcohol but I am not hopeful." Spray treatment was given daily for the first week and then at intervals of 3–4 days whenever the pain recurred. The patient lives in a hostel, and the spraying is carried out by the attendant in charge. He has now been relieved from severe pain for 15 months and says: "Lovely, wish I'd known about this before." He describes the treatment as "a godsend".

**Case 10.**—A woman, aged 69, had had post-herpetic neuralgia for $2^1/_2$ years, affecting right T12 and L1 dermatomes. Nine treatments with electroconvulsion had no effect. The first few spray treatments gave temporary and partial relief, and after 5 days the patient began to have increasing periods of complete relief for up to 12 hours. Eventually the patient had only occasional pain and did not really need the spray but asked to have one to keep at home because, she said, "it did me the world of good".

## Discussion

It has not proved possible to devise a satisfactory form of controlled trial for skin-cooling treatment of post-herpetic neuralgia. The results described here indicate that the method is worth trying.

None of these patients had had satisfactory relief from any previous therapy other than by percussion with an electric vibrator. Percussion, however, is unsatisfactory because it is liable to damage the skin. The spray technique is simple, harmless, and satisfactory. It has the great advantage that it can be carried out at home by the patient, a relative, or the district nurse; hence there is no need for persistent pain to be endured between visits to the doctor.

The mechanism by which the skin-cooling spray acts is uncertain, but it seems to be related to the intensity of afferent stimulation. This is supported by the lack of response when less intensive types of spray, such as the local-anæsthetic pack, were used instead of the coarse-nozzled general-anæsthetic pack. In this series of cases change to a milder type of spray has been the commonest cause of relapse. The patients did not appreciate the

significance of the change from one type of spray to another, and this affords evidence that the results of treatment were not due to suggestion. In 3 cases a special mixture of 'Freon' in cans with a very strong spray * was substituted for ethyl chloride with satisfactory results. This mixture is not flammable, is not a general anæsthetic, and is not liable to freeze the skin. Such a preparation may prove more satisfactory for home use by non-medical persons.

I suggest that the relief of pain by cooling the skin depends on adequate afferent stimulation, and it is thus simply an example of the old therapeutic measure of counter-irritation. In 3 of the patients who did not respond the afferent stimuli may have failed to reach the central nervous system because of damage to the peripheral-nerve pathways by previous treatment. In post-herpetic neuralgia affecting the first division of the trigeminal nerve, such as was present in 4 of the successfully treated patients in this series, there is no evidence of the trigger areas or local muscular spasm postulated by Travell and Rinzler (1952).

**Summary**

Otherwise intractable post-herpetic neuralgia was treated by brief interrupted spraying of the affected area with ethyl chloride.

Of 16 cases 4 failed to respond, but 12 were satisfactorily relieved of pain for 3 to 21 months.

I am indebted to Dr. D. A. Cahal for supervising the treatment of 3 of the patients; and Dr. W. A. Bain, who first introduced me to the analgesic properties of cooling sprays, for his unfailing support and encouragement.

REFERENCES

Gooddy, W. (1957) *Brain*, **80**, 118.
Russell, W. R. (1959) *Proc. R. Soc. Med.* **52**, 983.
— Espir, M. L. E., Morganstern, F. S. (1957) *Lancet*, i, 242.
Travell, J., Rinzler, S. H. (1952) *Postgrad. Med.* **11**, 425.

# STERNOCLAVICULAR ARTHRITIS

BERNARD CRYMBLE
M.B. Durh., F.R.C.S.
SURGICAL REGISTRAR

M. THOMPSON
M.D. Durh., M.R.C.P.
CONSULTANT PHYSICIAN,
DEPARTMENT OF PHYSICAL MEDICINE

ROYAL VICTORIA INFIRMARY, NEWCASTLE UPON TYNE

ALTHOUGH the sternoclavicular joints may be involved in polyarticular disorders—e.g., rheumatoid arthritis (Rathicke 1937), osteoarthrosis (Buckler 1955), ankylosing spondylitis (Cruikshank 1951), and syphilitic arthropathy (Sundt 1948)—acute sternoclavicular arthritis as an apparently isolated lesion has received little attention.

Cyriax (1956) has described the features of sprained sternoclavicular joint consequent upon a fall. He emphasised that subluxation of the sternal head of the clavicle secondary to a ruptured ligament was especially likely in osteoarthrotic joints or in those which had been the site of bacterial infection.

Heine (1926) described degeneration of the cartilages of both sternoclavicular joints as an ageing process, but he regarded these changes as asymptomatic and commoner in men, and he thought they were not aggravated by trauma. Langen (1934) also regarded degenerative changes in sternoclavicular joints as inevitable after the age of 40, and Zimmer (1939) suggested that they were due to constant movements and were therefore usually more pronounced on the right. Westerman (1942) agreed that asymptomatic degenerative changes were common, but thought that symptoms could be provoked by heavy manual work, and that, in these cases, the right sternoclavicular joint was more liable to be involved.

Kowallik (1951) listed the features of painful and swollen osteoarthrotic sternoclavicular joints, and discussed their differential diagnosis from traumatic subluxation of the clavicle which, in his experience, was seen in young people only.

Sokoloff and Gleason (1954) studied the sternoclavicular joints at necropsy in eighty-five cases, twenty-one of which had had symptoms in these joints during life. They described in detail the degenerative processes, and found that the synovial membrane was not significantly involved; but their studies did not include any case of acute or severe osteoarthrosis of these joints.

Arlet and Ficat (1958) reported the case-histories of twelve women with osteoarthrosis including unilateral involvement of the sternoclavicular joint, eight of whom had presented with an isolated complaint of pain in this joint. These workers emphasised that the symptoms could be severe and chronic, and they had to resort to excision of the sternal head of the clavicle in two cases to relieve the intractable pain.

Between May, 1957, and March, 1958, nine patients—seven women and two men—presented at the casualty department of the Royal Victoria Infirmary with acute symptoms referable to one or both sternoclavicular joints, and they were later investigated in the department of physical medicine. The clinical features are summarised in the table. In cases 1–8 inclusive the following investigations were normal: erythrocyte-sedimentation rate; blood Wassermann and Kahn reactions; gonococcal fixation test; Rose-Waaler test; full blood-counts; and urine analysis.

PRINCIPAL FINDINGS IN NINE PATIENTS WITH ACUTE STERNOCLAVICULAR ARTHRITIS

| Case no. | Sex | Age (yr.) | Side involved | Immediate cause | Other clinical features | Response to local steroid injection |
|---|---|---|---|---|---|---|
| 1 | F | 57 | R | House cleaning | Heberden's nodes<br>Cervical spondylosis<br>Tennis elbow | Complete relief |
| 2 | F | 49 | L | Carrying ledgers | Osteoarthrosis of knees<br>Heberden's nodes<br>Hallux valgus | Complete relief |
| 3 | F | 49 | R | Carrying fruit trays | Osteoarthrosis of knees<br>Heberden's nodes | Complete relief |
| 4 | F | 52 | R | Carrying books | Heberden's nodes<br>Pericapsulitis of shoulder | Complete relief |
| 5 | F | 54 | R | Clipping a hedge | Osteoarthrosis of knees and trapeziometacarpal joints<br>Lumbar spondylosis | Improved, then cured after 2nd injection |
| 6 | F | 47 | L | Floor polishing | Osteoarthrosis of knees<br>Hallux valgus | Complete relief |
| 7 | M | 63 | L | Carrying steel girders | Spondylosis<br>Osteoarthrosis of knees | Complete relief |
| 8 | M | 63 | R | Loading lorries | Lumbar spondylosis | Complete relief |
| 9 | F | 57 | R and L | Carrying trays of dishes | Epilepsy<br>Tertiary syphilis | Not given. Responded to antisyphilitic therapy |

### Illustrative Case-reports

**Case 3.**—A widow of 49 started work in a factory in September, 1957. This entailed packing boxes of fruit and then carrying for several yards trays laden with these boxes (about 50 lb.) about 8 or 10 times daily. She began to have pain and

* Specially prepared by Smith, Kline & French Laboratories, Philadelphia, U.S.A., at the suggestion of Dr. W. A. Bain, director of the Smith, Kline & French Research Institute, Welwyn Garden City, England.

swelling in the right sternoclavicular region which persisted for 4 weeks, and then slowly improved with rest. The symptoms recurred in November, and she finally gave up her work in December. After that she was well until March, 1959, when she took a job as an ironer in a laundry and was again troubled with pain and swelling in the right sternoclavicular region. This responded to an intraarticular injection of hydrocortisone acetate 50 mg., and has not recurred.

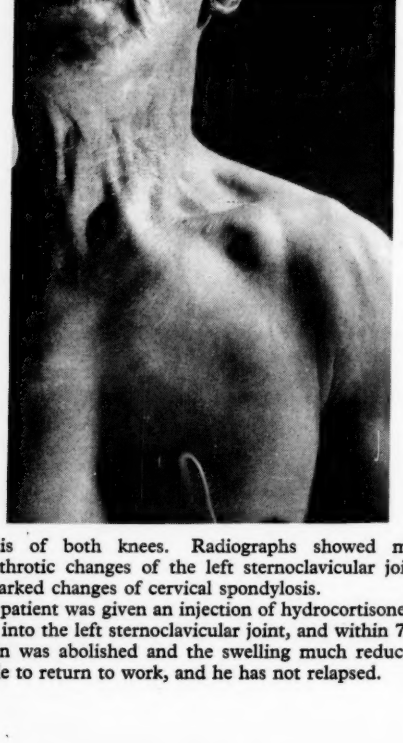
Examination revealed Heberden's nodes over the terminal phalanges of her hands, well-established osteoarthrotic changes in both knees, and subacute arthritis of the right sternoclavicular joint, with swelling, tenderness, and pain, and crepitus on movement. Radiographs showed mild osteoarthrotic changes of the right sternoclavicular joint, and undoubted osteoarthrotic changes in both knees. The lumbar spine, sacroiliac joints, and chest showed no significant abnormality.

**Case 5.**—A housewife, aged 54, had acute swelling and pain in the right sternoclavicular region in May, 1957, the day after mowing a lawn and clipping a hedge.

The physical signs suggested an acute sternoclavicular arthritis. Crepitus was elicited also in the left joint, which was symptom-free. She had osteoarthrotic changes in both knees and both trapeziometacarpal joints. Radiographs of the sternoclavicular joints were normal, but there was lumbar spondylosis and degeneration of the L5/S1 disc.

The patient was given an injection of hydrocortisone acetate 25 mg. into the right sternoclavicular joint, with much relief of symptoms. Her condition relapsed on Oct. 25 after exceptionally heavy housework, and her symptoms again responded to an injection of hydrocortisone acetate 25 mg. There has been no subsequent relapse.

**Case 7.**—A miner of 63, employed in fitting girders, had acute pain and swelling in the left sternoclavicular region in October, 1957, after a period of exceptionally heavy work. He carried the girders and held them in the left hand, imposing severe strain on the left arm and shoulder. Rest did not relieve his symptoms, and when he was referred to hospital on Nov. 16 he had signs of acute sternoclavicular arthritis on the left (see figure), and of cervical and lumbar spondylosis and osteo-



arthrosis of both knees. Radiographs showed moderate osteoarthrotic changes of the left sternoclavicular joint, and well-marked changes of cervical spondylosis.

The patient was given an injection of hydrocortisone acetate 50 mg. into the left sternoclavicular joint, and within 72 hours the pain was abolished and the swelling much reduced. He was able to return to work, and he has not relapsed.

**Case 9.**—A woman of 57, employed as a dishwasher, developed painful swelling in the left sternoclavicular region shortly after starting a new job where she had to carry heavy trays full of dishes. During the next 3 months she had similar symptoms and signs on the right, and she gave up her job. Her symptoms persisted despite rest, and she was referred to hospital in October, 1957, with bilateral signs of sternoclavicular arthritis, greater on the left. The swelling was firm, and was not an effusion. Radiographs of the sternoclavicular joints and spine were within normal limits. She had no other abnormal physical signs, but she had had occasional epileptic fits, well controlled by phenobarbitone, over 17 years.

The blood Wassermann reaction was strongly positive, and the diagnosis of syphilis was confirmed by a positive treponema-immobilisation test. The erythrocyte-sedimentation rate was normal. The patient was treated initially with potassium iodide gr. 15 t.d.s., and over 3 weeks the joint swellings regressed. With further antisyphilitic therapy improvement has been maintained.

## Discussion

The condition described in the first eight cases is obviously not uncommon, since all these patients were seen at one hospital department within 9 months. But in no case had the diagnosis been established before the patient was sent to hospital. The clinical features of sternoclavicular arthritis were those of a synovitis and capsulitis, with various degrees of effusion. Crepitus, when elicited, was apparently superficial and in keeping with soft-tissue thickening. It was not the coarse grating crepitus found with bony and cartilaginous erosions. Most of these patients, however, all of whom were over 45, had evidence of osteoarthrotic changes elsewhere.

Acute sternoclavicular arthritis is clearly different from sternoclavicular subluxation, in which the sternal end of the clavicle is displaced, forming a hard bony projection. None of the present series showed any evidence of subluxation clinically or radiographically. Furthermore subluxation of the sternoclavicular joint in the elderly is often without symptoms, and in the young is usually due to severe trauma.

The factor which seemed to precipitate symptoms in all our cases was unusual or undue strain on the joint, associated with heavy work. Even in case 9, with syphilis, there was a history of trauma to the sternoclavicular joints. In the two patients who relapsed, further lifting strains were implicated, and, except for case 9, the three patients with acute signs in the left sternoclavicular joint had been doing work which threw special strain on the left arm and shoulder. The side involved in our series—five right, three left, and one bilateral—supports the findings of Zimmer (1939) and Westerman (1942), but the high female/male sex-ratio (7/2) is not in keeping with the pathological observations of Heine (1926) on sternoclavicular joints. A striking fact is that no fewer than five of the seven women in our series were obliged to work, and they had either recently started work or were undertaking some unaccustomed task. The clinical adage of shoulder pain being commoner in " widows who take in washing " can in a modified way apply to acute sternoclavicular arthritis.

Only one patient had an underlying disease (case 9), but this example shows the necessity for investigation of acute sternoclavicular arthritis. In the other patients conditions such as tuberculosis, rheumatoid arthritis, ankylosing spondylitis, and other spondylitic syndromes were excluded. The only consistent findings were those of osteoarthrosis—of the hands in five patients, the spine in four, and the knees in five. The signs of degenerative

disease in the sternoclavicular joints were never severe, nor did the joint changes justify a diagnosis of generalised osteoarthrosis. The significance of concurrent degenerative joint changes in these eight patients is doubtful, since they were mostly asymptomatic and scrutiny of a comparable group of patients would certainly reveal appreciable evidence of osteoarthrosis. Nevertheless the weight of pathological evidence suggests that local degenerative changes in the sternoclavicular joints of people over 40 is of ætiological significance. In patients so predisposed, strain or unaccustomed use of the joint may provoke acute arthritis.

Once established, the arthritic signs and symptoms remain active, and the condition runs a chronic course. In our series the symptoms persisted for 2–12 weeks (average 7 weeks) before the patients were referred to hospital. Rest and avoidance of the provocative factors did not give relief, but all the patients gained striking and lasting benefit from the intracapsular injection of hydrocortisone acetate 25 to 50 mg. When further trauma provoked relapse, injection again proved effective.

**Summary**

Nine patients, all over 45, presented with acute sternoclavicular arthritis. One woman had chronic syphilis, and the arthritic signs receded with appropriate therapy. The other eight (six women and two men) had degenerative changes in the sternoclavicular joints and a history of trauma or strain involving the affected joint.

Degenerative changes are common in the sternoclavicular joints of people over 40, and acute arthritis with synovitis and capsulitis may be provoked by unaccustomed physical strain. The condition tends to become chronic, but intracapsular injection of hydrocortisone speedily proved effective in all cases.

REFERENCES

Arlet, J., Ficat, P. (1958) *Ann. rheum. Dis.* **17**, 97.
Buckler, W. St. J. (1955) *Ann. phys. Med.* **2**, 180.
Cruikshank, B. (1951) *Ann. rheum. Dis.* **10**, 393.
Cyriax, J. (1956) Orthopædic Medicine; vol. I, p. 190. London.
Heine, J. (1926) *Virchows Arch.* **260**, 521.
Kowallik, B. (1951) *Zbl. Chir.* **76**, 672.
Langen, P. (1934) *Virchows Arch.* **293**, 381.
Rathicke, L. (1937) *Dtsch. Z. Chir.* **249**, 162.
Sokoloff, L., Gleason, I. O. (1954) *Amer. J. clin. Path.* **24**, 406.
Sundt, H. (1948) *Acta derm. Venereol., Stockh.* **28**, suppl. 20, p. 67.
Westermann, H. H. (1942) *Arch. klin. Chir.* **203**, 19.
Zimmer, E. A. (1939) Das Brustbein und seine Gelenke; p. 55. Leipzig.

# NICOTINIC ACID IN THE TREATMENT OF ISCHÆMIC HEART-DISEASE

C. E. GOLDSBOROUGH
M.B. Durh.
GENERAL PRACTITIONER, ROTHWELL HAIGH, NEAR LEEDS

IN ischæmic heart-disease the levels of β-lipoproteins and cholesterol in the plasma are usually above normal. Many investigators have shown that these raised levels can be lowered by large doses of nicotinic acid (Altschul et al. 1955, Altschul 1956, 1958, Parsons et al. 1956, Parsons and Flinn 1957, Achor et al. 1958, Comesana et al. 1958).

Since 1946 I have been using nicotinic acid (combined with nicotinamide) in cases of acute myocardial infarction, angina of effort, and intermittent claudication. This paper refers mainly to 36 patients with angina and 24 with myocardial infarction, seen in a practice of 2900 people. After treatment with these vitamins attacks of anginal pain have steadily diminished, and in the large majority of cases have ceased entirely. In myocardial infarction, injection of nicotinic acid has usually been followed by dramatic relief of pain and anguish.

Nicotinic acid is a powerful vasodilator and has been used by a number of workers in the treatment of angina of effort. Side-effects such as flushing, vertigo, and even collapse, have caused many to dislike it, and results have varied:

Neuwahl (1942) gave a 0·5% intravenous infusion as a drip, having found the results of oral administration "uncertain". Brock (1942) reported that the immediate effect of giving nicotinic acid was "to relax spasm". Rook (1944) had good results in 14 out of 15 angina cases with intravenous nicotinamide. Moncrieff (1942), giving nicotinic acid by mouth in small doses, described its influence as "gratifying though irregular". From a controlled clinical trial in ten cases, however, Stokes (1944) regarded nicotinic acid as inferior to nitroglycerin as a vasodilator. After this it was rarely used in ischæmic heart-disease. Aleksandrow and Kodejsko (1949) recorded benefit in 10 out of 15 cases treated with daily infusions of nicotinamide.

All these results were based on small series of cases.

In 1946 I was searching for a vasodilator to replace nitroglycerin, which I found unsatisfactory (1) because it tended to induce headache (2) because its efficacy seemed to diminish with repeated use, and (3) because it did not seem to reduce the number of anginal attacks. Unaware of the above observations, I gave 50 mg. of nicotinic acid, by hypodermic injection, to a patient with acute myocardial infarction. The effect was surprising in that the pain was relieved in fifteen minutes.

Largely by trial and error, I developed a technique in which acute infarction was treated by both parenteral and oral administration of nicotinic acid and nicotinamide, and angina of effort with tablets.

## Treatment and its Results

Patients with a coronary thrombosis were given nicotinic acid 50 mg. hypodermically and 100 mg. under the tongue. In 18 out of 25 patients a response was obtained after the first injection, but in 16 of these further injections were needed to maintain relief. The response consisted in flushing of the skin, especially about the head and shoulders; this came on five to ten minutes after the injection and lasted for up to twenty minutes. Usually the face was most affected, the lips and cheeks becoming suffused. As the flush developed, the pain and shock subsided. Thus the shock might pass off very quickly, and it was striking to see a man who was grey and shocked become quite pink ten minutes after the injection. The pain might recur as the flush passed off. If it was severe, the injection was repeated; if it was moderate, 50 mg. nicotinic acid was given by the mouth, being repeated hourly as necessary. If no flushing occurred after the initial injection, two further injections were given at intervals of fifteen minutes. If there was still no reaction, heparin 15,000 units was given, and the patient sent to hospital; but this was necessary in only 2 cases in the present series. Morphine was avoided, because it was regarded as dangerous in coronary thrombosis. The injection of nicotinic acid was usually followed by its administration by mouth, 100 mg. thrice daily after food.

In angina of effort, nicotinic acid was given after food; for, with the doses employed (up to 200 mg. thrice daily), excessive vasodilatation was not uncommon, and this was minimised by administration on a full stomach. Both in

angina and in acute infarction, it was found that if half the dose was given in the form of nicotinamide a smoother and more sustained vasodilatation was obtained. The nicotinamide was given before food, because its vasodilator effect was thought to be considerably less than that of the acid. The dosage varied between 50 mg. and 200 mg. of each thrice daily (i.e., up to 1·2 g. of the combined vitamins daily). The usual maintenance dose was 150 mg. of each, but if necessary the dose could be doubled, tripled, or even quadrupled.

When vasodilatation was excessive, a condition like prickly heat occasionally developed, with pyrexia, itching, and considerable discomfort. Warning of this possibility was always given to the patient. He was told that the purpose of the treatment was to dilate the blood-vessels; that if this was achieved his face would flush; and that this was a desirable, expected, and harmless reaction. Only 3 patients had excessive vasodilatation, and to these nicotinic acid had to be given in graduated dosage. One patient fainted at the beginning of treatment: the usual flushing was followed by a rebound effect of pallor and syncope. Thus the treatment is not entirely without danger, and perhaps requires some experience. When this patient's dosage was reduced to 50 mg. (from 100 mg.), all was well, and subsequently 100 mg. thrice daily was taken without incident. Occasionally, if the patient reacted badly to nicotinic acid, nicotinamide only was used, in graduated dosage, and it was always well tolerated. One patient was hypersensitive to nicotinic acid, and went scarlet like a lobster, even to her eyeballs. She too was successfully put on nicotinamide.

As supplements, I usually gave other vitamins of the B group, and also ferrous gluconate.

After two or three years' continuous treatment many patients who had been unable to walk more than a dozen paces without severe angina had no further attacks, and some were able to resume fairly heavy manual work such as that of milk roundsman or bus-driver. Although this degree of improvement was more often seen in the 30–50 age-group, capacity for work often increased even in older people. One woman, aged 75, was an invalid when treatment of her severe angina was started in 1950; now, at 84, she is active and keeps house for her son. An outstanding effect of the treatment is the removal of the fear of impending death so common in angina, and also the fear of subsequent attacks.

In coronary infarction not all results, of course, have been good. 6 patients died, 4 from apparent massive thrombosis unresponsive to nicotinic acid. 2 others (one a man of 59, the other a woman of 82) seemed to get considerable relief from the injections but died suddenly.

4 of the angina patients also had intermittent claudication, and this was helped considerably by the nicotinic acid. This was therefore tried in peripheral vascular disorders, especially Buerger's disease. 3 patients with severe claudication and arterial obstruction demonstrated by arteriography recovered enough to resume their normal occupations.

2 patients with classical pulmonary embolism were treated with large doses of nicotinamide and antibiotics. They seemed to respond very satisfactorily.

## Diagnosis

Diagnosis both of angina and of coronary infarction was made on the history and clinical examination. As only 2 cases of coronary infarction were sent immediately to hospital, the electrocardiograms were usually obtained later—sometimes much later. Of the 25 cases diagnosed as infarction, 16 had electrocardiograms taken and all showed patterns indicating infarction. Of the 40 patients with angina, abnormal electrocardiograms were found in 12; but a normal electrocardiogram was not held to invalidate the diagnosis. A history of substernal pain on effort, radiating into the jaws or down the left arm, or a variation of this pattern of pain, was accepted, provided the pain was always induced by effort. A standard exercise-tolerance test was used to evoke the pain during examination.

## Illustrative Cases

*Coronary Thrombosis*

**Case 1.**—A man of 43, an insurance agent, had had increasing pain on effort since leaving the Army in 1946. On Oct. 10, 1947, he collapsed with substernal pain. He was pale and shocked when put to bed and given 50 mg. nicotinic acid hypodermically. Within ten minutes he became red in the face, and the pain subsided. The effect of this injection and the next one lasted about two hours, after which the pain returned, and was so severe that he lay supine and immobile, in fear of imminent death. He was given further injections and 100 mg. nicotinic acid every three hours by mouth. After a week the pain subsided; in eight weeks he was ambulant; and he resumed work three months later. Angina was still evoked by moderate exercise, but always relieved by nicotinic acid and nicotinamide taken by the mouth, which treatment was maintained for two and a half years, latterly intermittently.

On Jan. 3, 1951, about ten months after ceasing treatment, he had another infarction, for which he was given injections of nicotinic acid. This attack was much milder, and against orders he got out of bed on the seventh day, when he developed a further infarction. Recovery was fairly rapid with intensive treatment (three injections daily, with 150 mg. of both amide and acid thrice daily by mouth). During convalescence, he was put on oral nitroglycerin for a fortnight, but he insisted on having the nicotinic-acid treatment, which he said was far superior.

The angina has improved greatly. It is still evocable by excessive effort, but he won a prize as the champion agent for his firm in the West Riding, and he remains active and well, maintaining treatment to this day. With the angina he has had intermittent claudication, which is also controlled by the treatment.

**Case 2.**—A long-distance bus-driver, then aged 45, collapsed at the wheel July, 1949. After a night at hospital he was sent home. When seen, he could not move without substernal pain, and his face was pallid; blood-pressure 150/95 mm. Hg. He was given 150 mg. nicotinic acid and nicotinamide by mouth thrice daily, and within a week his substernal pain and fear of something about to happen had disappeared. He was ambulant after a week, and after a further month he returned to his work of tours bus-driver. Treatment was maintained for two years quite regularly, and his angina ceased; but he disliked the discipline of constant regular treatment, and finally abandoned it.

Gradually the angina returned, and in 1954 he had a severe attack of coronary thrombosis. This time it occurred at night, and I was sent for. He was ashen, immobile, and afraid to move; he spoke in a whisper and thought he was about to die. He was given successive injections of 50 mg. of nicotinic acid, with oral treatment of both acid and amide 100 mg. each thrice daily. After a rapid recovery, treatment was maintained for three years and his angina again disappeared. Treatment then ceased. In 1957 his angina again returned fairly severely, and he came for further treatment. This time an electrocardiogram was taken before treatment, and it showed a grossly abnormal pattern: the cardiologist commented that it was very unusual for a

patient with so abnormal a pattern to be so well nine years after the original and obviously severe infarction. Having rapidly responded to treatment, he maintains it conscientiously and has been well since. He continues his bus-driving.

**Case 3.**—A man now aged 62, a bus-driver, had a history of thyrotoxicosis ten years before, in 1946. In 1950, having gradually developed angina of effort, he was put on nitroglycerin tablets for a month without any benefit. He had an irregular pulse, 110 per min., and complained of substernal pain on effort, radiating into the jaws and down the left arm; blood-pressure 190/100. On nicotinic acid and nicotinamide he improved steadily, his anginal attacks going down from four a day to about twice a week; his range of effort became normal. After twelve months he became careless with his treatment, thinking that he was cured; but he maintained it intermittently for about three years.

Called to see him on Dec. 19, 1955, I found him grey, with acute air-hunger, a blood-pressure of 90/60, and a feeling of tightness in his chest, though without pain. Coronary thrombosis was diagnosed; and he was given two successive injections of nicotinic acid 50 mg. which relieved him considerably, and he was put on 450 mg. each of acid and amide which relieved him considerably. He was in bed for two weeks, and later an electrocardiogram demonstrated "unequivocal infarction". A cardiologist said that he would never work again as a bus-driver; but after three months he resumed his occupation and he has been driving continuously since. He is always careful to maintain treatment.

**Case 4.**—This lady was first seen in 1953, when she was 68 years of age and had typical angina of effort—severe enough to make her think of impending death. After three months' treatment with nicotinic acid and nicotinamide she was able to resume her duties as a magistrate; but she then became careless and ceased treatment. Early in 1954 she had a coronary thrombosis with shock, collapse, a drop in blood-pressure, and pain. She was given one injection only of nicotinic acid, followed by oral treatment with acid and amide, and also pyridoxine (300 mg. daily of each). She has carefully maintained treatment since then and keeps very well. She also had intermittent claudication of the left leg which began before the infarction, but which cleared up completely. It recurred when treatment was neglected.

**Case 5.**—At 66 years of age, this patient collapsed with a coronary thrombosis within the precincts of a hospital. She was kept in bed a month, and was treated with anticoagulants very successfully; but when she came home she still had angina when lying down, with angor animi. For a month she was kept on the hospital-recommended treatment of 'Mycardol': when this was changed to nicotinic acid and nicotinamide the difference was apparent. Her dyspnœa diminished and her angor animi disappeared very rapidly. In twelve months she was able to do a full housekeeping job. She has intermittent claudication of the left leg, which has not cleared up completely but does not prevent her from earning her living.

*Angina of Effort*

**Case 6.**—In 1950 this patient, then aged 50, had a blood-pressure of 230/120, an apex-beat in the anterior axillary line, and irregular rhythm with filling of the neck veins, gross albuminuria, gross dyspnœa of effort, and typical attacks of angina brought on by the slightest exertion. She was put on nicotinic acid and amide, 100 mg. of each thrice daily, with extra nicotinic acid for attacks of severe pain. She was also given digoxin 0·5 mg. daily, vitamin $B_1$ 10 mg., and pyridoxine 10 mg., thrice daily. Her blood-pressure is now 170/100, her dyspnœa is very slight, and she gets no pain at all. Eight years ago she could not walk a dozen yards without acute dyspnœa; yet she manages a successful grocery shop.

**Case 8.**—A cinema attendant with labouring duties developed tightness of the chest and pain on effort and he consulted me six months later, in April, 1957. He was 52 years of age. After electrocardiography a cardiologist reported that he had ischæmic disease, and advised nitroglycerin. After three weeks of this his attacks of pain were fewer, but its severity was undiminished and he had headache almost every time he took enough nitroglycerin to relieve his pain. He was then put on nicotinic acid and amide 100 mg. each, thrice daily. His pain steadily diminished, and eventually disappeared. His electrocardiogram has reverted to normal.

## Discussion

The response to nicotinic acid seems to depend on the stage of the infarction. When thrombosis is well established, little can be hoped from nicotinic acid or any other vasodilator. Thus in cases of massive thrombosis, and also perhaps in the elderly, anticoagulants remain the best means of treatment.

I have been impressed by the way in which the tendency to thrombosis has varied: in the younger patients spasm seemed to predominate. It is well known that in a proportion of cases no thrombosis can be demonstrated after a fatal infarction.

The fact that nicotinic acid is known to lower plasma-cholesterol levels (as was also seen in those of my cases where the cholesterol content of the blood was estimated) suggests that, unlike the nitrites, it does not act solely as a vasodilator. Though the doses found effective are far larger than those sufficient for relieving the kind of deficiency which causes pellagra, I believe that the concept of ischæmic heart-disease as a deficiency disease is worth pursuing. But my purpose here is simply to draw attention to the clinical efficacy of nicotinic acid as apparent in the cases treated in my practice during the past fourteen years. If the administration of nicotinic acid could give protection against the rising incidence of angina of effort and of coronary thrombosis, its more general use could be important.

## Summary

Since 1946, 60 cases of ischæmic heart-disease (24 of infarction and 36 of angina of effort) have been treated with large doses of nicotinic acid and nicotinamide.

Injection of these remedies often give rapid relief in cases of myocardial infarction (especially where arterial spasm is a more important element than thrombosis), and on maintenance treatment with smaller doses by mouth many patients with angina have ceased to have attacks.

Given in large doses, nicotinic acid is a potent vasodilator, which must be used with caution. The fact that it lowers plasma-cholesterol levels suggests, however, that the benefit observed in cases of ischæmic heart-disease cannot be entirely ascribed to vasodilatation.

My thanks are due to Prof. R. E. Tunbridge for comments on an earlier draft of this paper. I am also grateful to Dr. H. T. Levi for repeated advice, encouragement, and criticism, and to Mrs. Abbishaw for her secretarial help.

REFERENCES

Aleksandrow, R., Kodejsko, E. (1949) *Pol. med. Wkly*, **4**, 1089.
Achor, R. W., Berg, K., Barker, N. W., McKenzie, B. F. (1958) *Circulation*, **17**, 497.
Altschul, R. (1956) *Z. KreislForsch.* **45**, 573.
— (1958) *J. Amer. med. Ass.* **168**, 822.
— Hoffer, A., Stephen, J. D. (1955) *Arch. Biochem. Biophys.* **54**, 558.
Brock, G. (1942) *Lancet*, ii, 587.
Comesana, F., Nova, A., Fishleader, B. L., Sodi-Pollares, D. (1958) *Amer. Heart J.* **55**, 476.
Moncrieff, A., (1942) *Lancet*, i, 633.
Neuwahl, F. J. (1942) *ibid.* ii, 419.
Parsons, W. B., Achor, R. W., Berg, K., McKenzie, F. B., Barker, N. W. (1956) *Proc. Mayo Clin.* **31**, 377.
— Flinn, J. H. (1957) *J. Amer. med. Ass.* **165**, 234.
Rook, H. C. (1944) *Lancet*, ii, 864.
Stokes, W. (1944) *Brit. Heart J.* **6**, 157.

# CHROMOSOME TRANSLOCATION AS A CAUSE OF FAMILIAL MONGOLISM

C. O. CARTER
B.M. Oxon., M.R.C.P.

OF THE MEDICAL RESEARCH COUNCIL'S CLINICAL GENETICS RESEARCH UNIT, INSTITUTE OF CHILD HEALTH, GREAT ORMOND STREET LONDON, W.C.1

J. L. HAMERTON
B.Sc. Lond.

P. E. POLANI
M.D. Pisa, M.R.C.P.

A. GUNALP *
M.D. Ankara

OF THE MEDICAL RESEARCH UNIT, NATIONAL SPASTIC SOCIETY, DEPARTMENT OF CHILD HEALTH, GUY'S HOSPITAL, LONDON, S.E.1

S. D. V. WELLER
M.D. Lond., M.R.C.P.

CONSULTANT PÆDIATRICIAN, BROMLEY AND DARTFORD HOSPITAL GROUPS

EARLIER this year Polani et al. (1960), examining the chromosomes of three mongols born to young mothers, found that one of these mongols had 46, not 47 chromosomes. There were two chromosomes of pair 21, but one member of pair 14 (Standard System) was of unusual length and morphology. They postulated that this abnormal chromosome had arisen by means of a translocation between a chromosome 14 and a chromosome 21, and noted that this would provide a mechanism for familial mongolism. Subsequent examination of peripheral blood has shown (J. L. H.) that, in fact, the parents had a normal chromosome complement; therefore the translocation and non-disjunction in this patient must have occurred during gametogenesis in one of the parents or, less likely, in the embryogenesis of the child.

A large number of families of mongol patients attending The Hospital for Sick Children have been followed for up to ten years, and one of these families was felt to be the most suitable for testing the hypothesis that translocation might provide a mechanism by which some apparently normal parents are predisposed to have mongol children.

* Present address: Haceteppe Children's Hospital, Ankara, Turkey.

## Investigation

### *The Family*

A pedigree of this family is shown in fig. 1.

The index patient M.A. (III.2 in the pedigree) attended The Hospital for Sick Children in 1952 at the age of one year and the diagnosis of mongolism was confirmed. In addition to the usual facial stigmata (see fig. 2), his palm prints were characteristic of mongolism [summed a t d angles at the age of 9 years are 166°, the mean in normal children being 88°±16° (Penrose 1954)].

This boy is an imbecile who now attends an occupation centre. He has no other congenital malformations. In November 1953, M.A.'s mother (II.6) had another boy (III.3) who died of congenital heart disease at the age of 5 months. He, too, was a mongol. The third boy (III.4), born in October, 1958, is normal. In September, 1958, M.A.'s maternal aunt (II.3) had her first and only child, a boy (III.1) who died at the age of 5 hours, probably of birth injury, and was also noted to be a mongol. Neither M.A.'s mother nor his aunt have had any miscarriages. Both these women and their mother (I.1) were of at least average intelligence and fitness.

CHROMOSOME-COUNTS IN THE INDEX PATIENT (M.A.) AND HIS RELATIVES

| — | Diploid number | Chromosome-counts <45 | 45 | 46 | 47 | Total cells | No. of cells analysed |
|---|---|---|---|---|---|---|---|
| M.A. (III.2) .. | 46† | 3* | — | 25 | 2* | 30 | (6) |
| Mother (II.6) .. | 45† | 9* | 27 | 3* | — | 39 | (6) |
| Mother's mother (I.1) .. .. | 45† | 3* | 8 | — | — | 11 | (2) |
| Mother's sister (II.3) .. .. | 45† | 8* | 7 | — | — | 15 | (3) |
| Father .. .. | 46 | — | — | 15 | — | 15 | (3) |
| Brother .. .. | 46 | 17* | 6* | 20 | — | 43 | (6) |

† Translocation present. * Cells broken.

M.A. had two maternal uncles (II.1 and 2) and two further maternal aunts (II.4 and 5), all of whom had died in infancy of bronchitis or bronchopneumonia. The death certificates of these children do not mention mongolism, but this does not exclude the possibility that one or more of them were mongols.

### *The Findings*

The chromosome analyses were made from short-term cultures of peripheral blood by a modification of the technique of Hungerford et al. (1959). The Standard System (Denver) of nomenclature (*Lancet* 1960) was used. The chromosomes of M.A., his surviving brother, his mother, father, maternal aunt, and maternal grandmother were examined. The counts are summarised in the table.

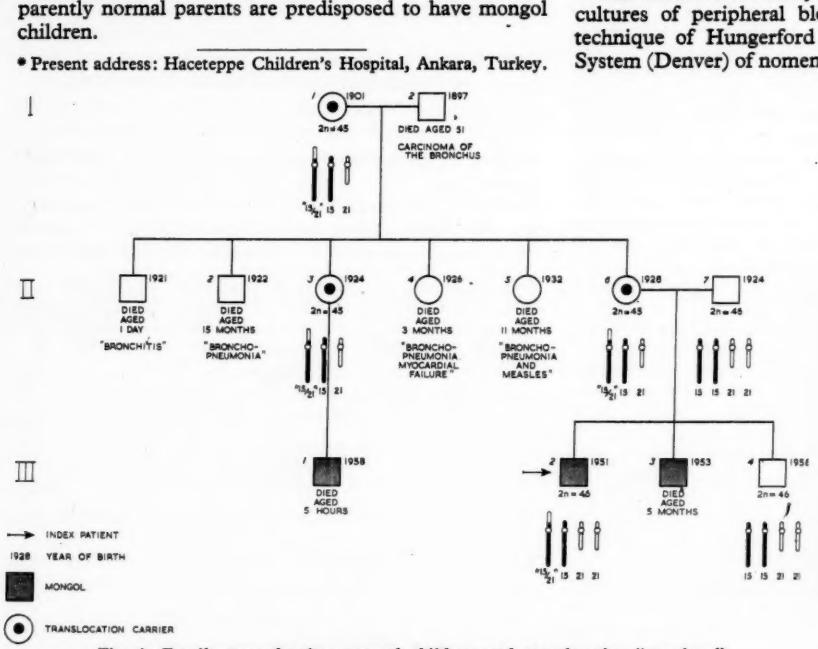



Fig. 1—Family tree showing mongol children and translocation "carriers".

Fig. 2—The index patient.

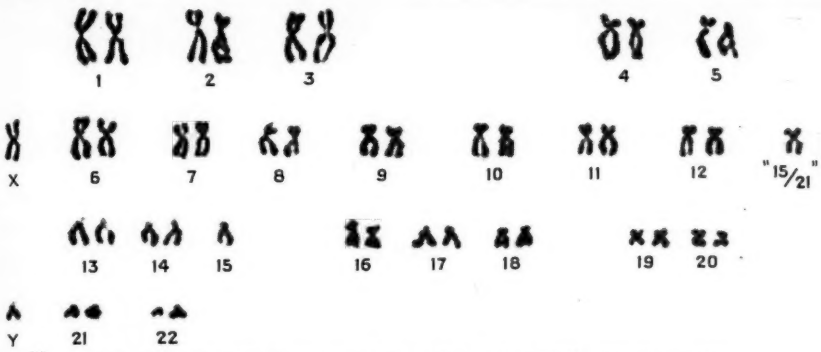



**Fig. 3—Analysis of the karyotype of the index patient (III.2)—Standard System.**

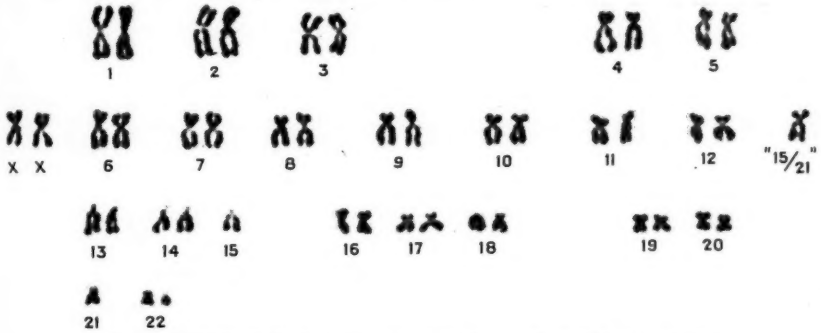



**Fig. 4—Analysis of the karyotype of the mother (II.6)—Standard System.**

M.A's count was 46. Those of his mother, maternal aunt, and maternal grandmother were all 45. His father's (II.7) and brother's counts were 46, with normal chromosomes. M.A.'s karyotype is shown in fig. 3.

This shows only 4 chromosomes in the 21–22 group plus one Y chromosome, as in a normal male, whilst in the 13–15 group 5 instead of 6 chromosomes were observed. In group 6–12, an additional submetacentric chromosome was seen.

The karyotype in M.A.'s mother (fig. 4) was identical with that of her sister and her mother.

This shows only 3 chromosomes instead of 4 in the 21–22 group, 5 instead of 6 in the 13–15, and an additional chromosome in the group 6–12 similar to that seen in M.A.

The 6–12 groups of the four individuals are shown together in fig. 5, and the similarity of the additional chromosome in this group in each individual may be seen.

*Interpretation*

Because mongolism appears to require the presence in triplicate of the genetic material of chromosome 21, it is logical to assume that this is also the case in patient M.A. We therefore consider that the additional chromosome in the 6–12 group in all four individuals has arisen by means of a translocation, probably between chromosomes 21 and 15, at least as early as gametogenesis in the maternal grandmother's parents, or the embryogenesis of this grandmother. Examination of the additional chromosomes suggests that it is the same chromosome being inherited throughout the family.

The suggested mechanism for the translocation and its inheritance is shown in fig. 6.

It is, however, by no means certain that the four possible types of gamete will occur with equal frequency. This will be greatly influenced by the pairing behaviour of the translocation at meiosis.

**Discussion**

The clinical interest of the finding of "carriers" of a translocation, which may cause mongolism, is that it may make it possible both to be more precise in advising parents on the risks of their having a second mongol child, and to detect relatives of mongols who themselves have high risks of having mongol children. Experience at The Hospital for Sick Children has shown that the risk of parents having a second mongol child is almost certainly raised above the random risk, especially at the younger maternal ages. It has not, however, been possible to show whether this is in most part an overall increase, or whether there are two groups of mongols, a majority with little, if any, increase in the risk of recurrence, and a minority with a relatively high risk. It is now important to discover, by systematic study, the extent to which the rare occasions in which one or other parent has an abnormal karyotype may account for the overall increased risk of recurrence of mongolism.

It is, perhaps, surprising that the "carriers" of the

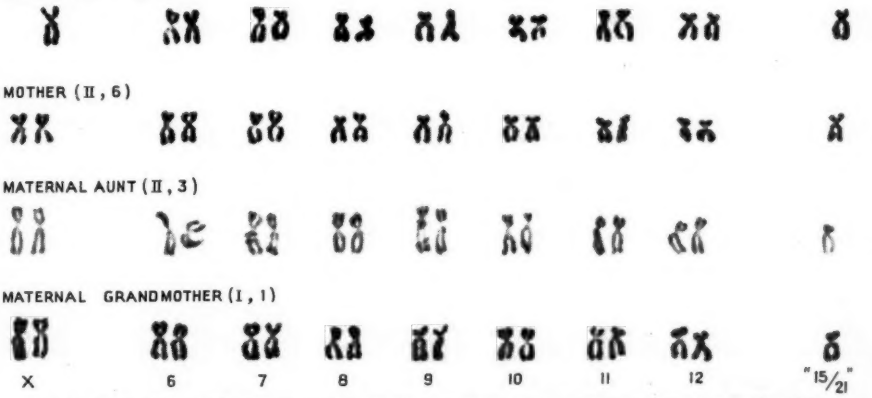



**Fig. 5—Comparison of the 6-12 groups in the four members of the family carrying the translocation.**

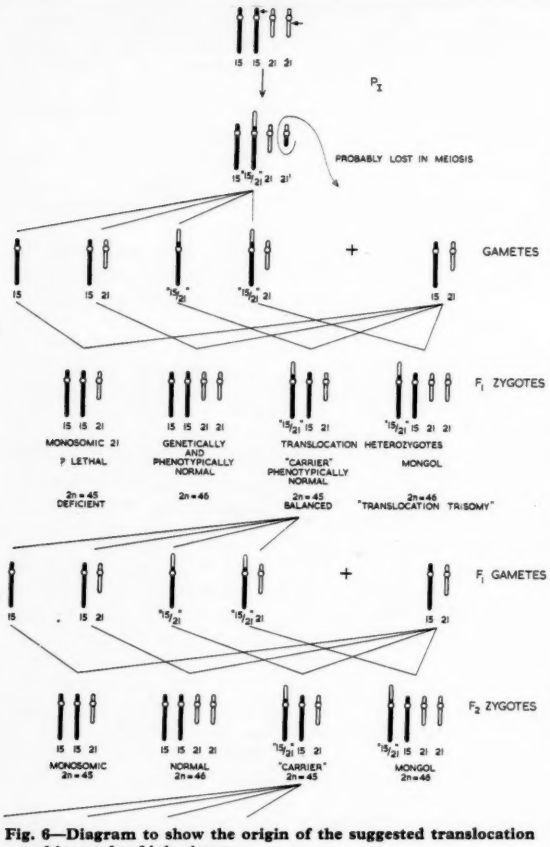



**Fig. 6—Diagram to show the origin of the suggested translocation and its mode of inheritance.**

translocation are apparently normal. They have, however, presumably lost very little chromosome material, only part of the two short arms of chromosomes 15 and 21.

There are two other instances in which the parent of a mongol child has been found to have an abnormal karyotype. In the first family (Fraccaro et al. 1960) the father is reported to have had 47 chromosomes; it is difficult to interpret the situation in this family. In the other family the situation appears from the preliminary communication (Penrose et al. 1960) to be very similar to that in the present family.

It is noteworthy that all the examples of presumed chromosome translocation that have been reported in man involve the acrocentric chromosomes, which tend to lie close together at interphase in association with the nucleolus (Polani et al. 1960).

### Summary

A family is described in which a translocation, probably between chromosomes 15 and 21, occurring at least as early as the embryogenesis of the grandmother, was responsible for mongolism in three of her grandchildren and possibly one or more of her children. Further studies are needed to see what proportion of the overall increased risk of recurrence of mongolism in later siblings is due to such recognisably abnormal karyotypes in a small minority of the parents of mongol children.

We should like to thank the members of the staff of The Hospital for Sick Children for access to their patients, Dr. J. A. Fraser Roberts for advice and encouragement, and Miss V. M. McGuire, Miss A. Horsley, and Mr. S. L. Yapp for their skilled technical assistance.

#### REFERENCES

Fraccaro, M., Kaijser, K., Lindsten, J. (1960) *Lancet*, i, 724.
Hungerford, D. A., Donnelly, A. J., Nowell, P. C., Beck, S. (1959) *Amer. J. hum. Genet.* **11**, 215.
*Lancet* (1960) i, 1063.
Penrose, L. S. (1954) *Ann. hum. Genet.* **19**, 10.
— Ellis, J. R., Delhanty, J. (1960). *Lancet*, ii, 409.
Polani, P. E., Briggs, J. H., Ford, C. E., Clarke, C. M., Berg, J. M. (1960) *ibid.* i, 721.

## RENAL MEDULLARY NECROSIS FOLLOWING EXSANGUINATION IN INFANCY

I. M. MARKS *
M.B. Cape Town
REGISTRAR, DEPARTMENT OF PATHOLOGY, UNIVERSITY OF CAPE TOWN

NECROSIS of the renal papillæ is diagnosed usually post mortem, but occasionally during life (Robbins and Angrist 1949, Swartz 1954, Cates and Hewer 1956). Many of the reported cases have been in diabetics with acute pyelonephritis; in non-diabetics the condition is usually associated with urinary obstruction and superimposed infection. Recently phenacetin consumption has been associated with papillary necrosis as part of a true chronic interstitial nephritis (*British Medical Journal* 1960).

Papillary necrosis in infancy without pyelonephritis or urinary obstruction has rarely been reported. One of the cases described by Swartz (1954) was a 5-month-old infant with *Pseudomonas aeruginosa* meningitis, cerebral atrophy, and bilateral papillary necrosis. This disorder was also noted by Morison (1945) in renal-vein thrombosis in the newborn.

The following case does not resemble the hitherto published cases of renal papillary necrosis in adults, except case 7 of Swartz and Hoogstraten (1959), where, in a woman, shock incidental to trauma to the right kidney led to bilateral papillary necrosis. The lesion is similar in distribution to that in the infant described by Swartz (1954).

### Case-report

The infant, a Bantu female, was born on the morning of Aug. 14, 1959; no details were available. At 5 P.M. that day the infant was brought to a maternity home, pulseless and exsanguinated, having bled from the umbilical cord. A rapid transfusion was given of 180 ml. of group-O rhesus-negative blood, not cross-matched as the infant was moribund. The infant responded well. 2·5 mg. of 'Synkavit' (a vitamin-K analogue) was given intramuscularly. That night the infant bled from the mouth and vagina, and was given a further 5 mg. of synkavit intramuscularly. After being quite well for the following two days, the infant suddenly died.

*Necropsy*

Postmortem examination was carried out four days after death (the body was refrigerated). Weight 2914 g., length 49 cm. The body was that of a full-term infant.

*Lungs* (right 20 g., left 17 g.) showed subpleural hæmorrhages and congestion. *Kidneys* (20 g.) showed no special external features. The capsules stripped easily. On section all the renal pyramids and inner portions of the medulla were strikingly pale yellow-white, contrasting vividly with gross congestion at the corticomedullary junctions (fig. 1). The cortex was paler pink than usual. The medulla of both kidneys was diffusely, uniformly affected. No thrombosis was evident in the inferior vena cava, the main renal veins at the hila, or their branches, but the junctions of the main renal veins with the inferior vena cava were not dissected. *Stomach* showed

* Present address: Maudsley Hospital, London, S.E.5.

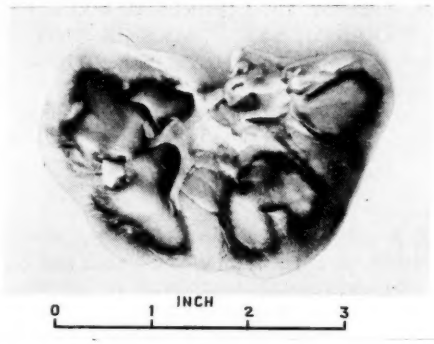



**Fig. 1—Section through kidney, showing diffuse nature of the process with hyperæmia and hæmorrhage at corticomedullary junction and pallor of medulla.**

notable changes. Mainly in the body and lesser curvature were numerous submucosal hæmorrhagic nodules up to 0·5 cm. in diameter, often confluent, and covered with yellow-grey exudate. Intervening mucosa was œdematous. Smear showed numerous gram-positive bacilli. *Large intestine* contained three similar areas. *Small intestine* was normal. The other organs showed no abnormal features.

*Microscopic Findings*

*Kidneys* showed complete coagulative necrosis of the entire inner medulla and papillæ, involving the collecting tubules and some loops of Henle (fig. 2). The outlines of the tubules were well preserved, the tubules being filled with dead cells, many having faded nuclei. There was slight patchy cellular reaction of histiocytes and polymorphs. In the medulla adjacent to the

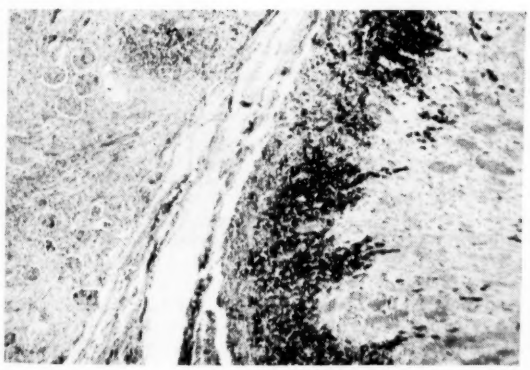


**Fig. 2—Low-power view of section from kidney, showing, from left to right, relatively intact cortex, arcuate artery, zone of hyperæmia and hæmorrhage, and necrosed medulla.**

necrotic area was a zone of hæmorrhage, merging with a zone of intense hyperæmia with dilated capillaries, and viable loops of Henle and collecting tubules. Some glomeruli were filled with blood, others were bloodless; but all were intact. Near the boundary zone some proximal and distal tubules of the cortex were necrotic in an irregular, patchy fashion. The bulk of the cortex, however, showed no abnormal features. The process was identical in both kidneys. No organisms were revealed by Gram's stain. Section through the renal hila showed normal veins and arteries with no thrombosis. *Lungs* showed congestion and intraatrial hæmorrhages. Some atria contained a faint hyaline membrane. *Stomach* contained numerous submucosal and mucosal hæmorrhages. Thrombosed submucosal veins were present. Mucosa above this was necrotic (or autolysed), and covered by exudate containing fibrin and scanty degenerate polymorphs, gram-positive bacilli, and gram-positive cocci. *Colon* was similar to stomach. *Uterus* showed hæmorrhagic endometrium with no glandular structures. Sections of other organs showed no special features.

## Discussion

*Renal Findings*

The most striking feature in this case was the renal lesion. The medullary and partial tubular necrosis was of very recent origin. No signs of infection were present. The bilateral uniform distribution pointed strongly to a vascular change

In the infant described by Swartz (1954) the distribution of the renal changes was similar, but thrombi were prominent in the intrarenal veins. In renal vein thrombosis there was usually gross congestion and hæmorrhage affecting most of the renal medulla and some of the cortex. In the present case, though the entire lengths of the renal veins were not dissected out towards the inferior vena cava, the vessels at the hila were not thrombosed, nor were the intrarenal veins thrombosed microscopically, and the inferior vena cava was normal. This case is therefore rather different from that of Swartz and those of Morison (1945).

The profound hypotension soon after birth may have been crucial in the pathogenesis of the renal lesion. Persistent renal vasospasm after hypotension is well known. On this basis lengthy oligæmic shock has often been followed by acute tubular necrosis, but medullary necrosis has not been attributed to this mechanism. In case 7 of Swartz and Hoogstraten (1959) shock with consequent vascular stasis in the renal medulla was suggested as a causal factor. The papillæ have a poor blood-supply compared to the rest of the kidney, but are less active functionally, which may partly explain why papillary necrosis has not been reported in these states. In the majority of reported cases, only with infection and/or renal obstruction has papillary necrosis developed. In the present case proximal tubules were necrosed, but the medulla was mainly affected. If the usually accepted type of hypotensive vasospasm is operative in neonates, why was the ensuing lesion here so paradoxical? It is also an interesting reverse of the cortical necrosis of the kidneys found sometimes in concealed accidental intrauterine hæmorrhage. Vasospasm may possibly have differed from the usual pattern by involving medullary rather than cortical arteries and arterioles.

*Similarity to Experimental Lesions*

Experimentally renal medullary necrosis has been produced in animals by the injection of tetrahydroquinoleine (Rehns 1901), vinylamine (Levaditi 1901, Mandel and Popper 1951), bromethylaminbromhydrate (Oka 1913), and mono-*N*-methyl-alanine (White and Mori-Chavez 1952). In the rabbits injected with vinylamine by Mandel and Popper (1951) ischæmic medullary necrosis developed, attributed to tissue anoxia caused by excessive medullary hyperæmia, vasoparalysis, and multiple thrombus formation. In the present case the lesions closely resemble the lesions of these rabbits in the early stages, except for the absence of thrombosis. Thrombosis in the rabbits might have been a secondary feature, stasis being the primary damaging factor—which would suggest that in both instances a similar vascular response occurred to different stimuli.

In rabbits Sheehan and Davis (1959), after applying a complete pedicle clamp to the kidney, found that the incidence of failed reflow through the medulla was

directly related to the duration of the initial ischæmia, reflow never occurring after clamping more than two hours. This failure was unrelated to death of the tubules. Medullary tubules could survive a two-hour period of ischæmia, and, if circulation was re-established at that time, most remained alive. Sheehan and Davis concluded that, when the medulla had become infarcted, it had been alive at the end of the period of pedicle-clamping and that it died subsequently because circulation was not re-established through it, for reasons unknown. In the present case, though no glomerular changes were noted, the similar renal findings support an ischæmic origin.

The possibility remains of a toxic cause of the renal lesion, perhaps operating through a vascular mechanism. The only drug known to have been given to the infant—synkavit—is not known to result in this lesion. The clinical and pathological course was not that seen in massive hæmolysis after blood-transfusion. Lastly, a gastrointestinal infection (see below) may have caused septicæmia or toxæmia, or both, acting selectively mainly on the renal medulla. The features here do not confirm this, but notoriously neonatal septicæmia can be undiagnosable except bacteriologically.

*Bleeding from Multiple Sites*

The initial hæmorrhage in this infant was from the umbilical cord, no cause for which was apparent. Blood-transfusion was followed by bleeding from the mouth and vagina. The vaginal bleeding probably followed endometrial changes due to œstrogen withdrawal after birth. The gastrointestinal and pulmonary hæmorrhage seen at necropsy may have been secondary to uræmia. The blood-urea was not estimated, but, as the infant died two days after the initial catastrophe, and as, judging from the histological findings, practically no renal function was possible, some uræmia may reasonably be assumed. Hæmorrhage from the gastrointestinal tract may occur in uræmia in children (Nelson 1954).

The gastrointestinal changes may have been infectious in origin; but unfortunately the exudate was not cultured, and only histological assessment has been possible; and this was difficult owing to severe necrosis or autolysis.

**Summary**

In a case of bilateral renal medullary necrosis in a neonate, the lesion apparently differed from the papillary necrosis usually found in adults, but resembled lesions produced in rabbits by injection of vinylamine or by complete clamping of the renal pedicle. Ischæmia following exsanguination is thought to underlie the lesion.

My thanks are due to Prof. J. G. Thomson and Dr. C. J. Uys for their valuable advice, and to Dr. M. Berman for the photographs.

REFERENCES

*British Medical Journal* (1960) i, 714.
Cates, J. E., Hewer, T. F. (1956) *ibid.* i, 1005.
Levaditi, C. (1901) *Arch. int. Pharmacodyn.* **8**, 45.
Mandel, E. E., Popper, H. (1951) *Arch. Path.* **52**, 1.
Morison, J. E. (1945) *Arch. Dis. Child.* **20**, 129.
Nelson, M. (1954) Textbook of Paediatrics; p. 1092. London.
Oka (1913) *Arch. path. Anat.* **214**, 149.
Rehns, J. (1901) *Arch. int. Pharmacodyn.* **8**, 199.
Robbins, E. D., Angrist, A. (1949) *Ann. intern. Med.* **31**, 773-793.
Sheehan, H. L., Davis, J. C. (1959) *J. Path. Bact.* **78**, 374.
Swartz, D. (1954) *J. Urol.* **71**, 385.
— Hoogstraten, J. (1959) *Brit. J. Urol.* **31**, 419.
White, J., Mori-Chavez, P. (1952) *J. nat. Cancer Inst.* **12**, 777.

"... And, please recall that the so-called art of medicine is a supplement, not a substitute, for science."—WILLIAM ENGSTROM, *Marquette med. Rev.* 1957–58, **23**, 3.

# EFFECT OF INTERFERON ON EXPERIMENTAL VACCINIA AND HERPES-SIMPLEX VIRUS INFECTIONS IN RABBITS' EYES *

KARI CANTELL
M.D. Helsinki

VEIKKO TOMMILA
M.D. Helsinki

*From the State Serum Institute and the Helsinki University Eye Hospital, Helsinki, Finland*

THE inhibiting effect of interferon (Isaacs and Lindenmann 1957) on the multiplication of various viruses in tissue cultures and in chick embryos has been clearly demonstrated (Henle et al. 1959, Ho and Enders 1959, Isaacs 1959, Porterfield 1959, Wagner 1960). But the activity of interferon in vivo has so far been proved only by its ability to inhibit locally the development of vaccinia lesions in rabbit skin when injected before or along with the virus (Lindenmann et al. 1957, Isaacs and Westwood 1959).

In this paper we describe the effect of interferon on the course of experimental vaccinia and herpes-simplex infections in the rabbit's eye.

## Material and Methods

*Preparation of Interferon*

Trypsinised rabbit-kidney cells were grown in Roux bottles in 70 ml. of the following medium: 40% Hanks' solution and 60% of a mixture containing equal amounts of the aminoacid constituent of Parker's solution, and pooled inactivated Seitz-filtered human serum. When uniform sheets of cells were obtained the medium was replaced with the following maintenance medium: 50% Hanks' solution, 47·5% of the aminoacid constituent of Parker's solution, and 2·5% inactivated filtered calf-serum.

The Enders strain of mumps virus was used for the production of interferon. The dialysed virus allantoic fluid was inactivated by ultraviolet irradiation, using a similar method to that described by Henle and Paucker (1958). In our hands, irradiation for 45+45 sec. made the virus non-infective for chick embryos.

The cell-cultures were seeded with 35 ml. of irradiated virus (1024 hæmagglutinating units per ml.) and 35 ml. of maintenance medium. After 3 hours' incubation at +37°C the cultures were washed five times and refed with 70 ml. of maintenance medium. The bottles were then further incubated for 24 hours at +37°C, and the medium was collected after vigorous shaking. This was ultracentrifuged for 60 min. (Spinco model L) at 34,906–73,300 *g*. The supernatant served as interferon. The interfering factor liberated by identical virus treatment of human cell-cultures matched the properties of interferon (Cantell 1960).

Control preparations were made in exactly the same way but using normal allantoic fluid instead of irradiated virus.

*Experiments on Rabbits' Eyes*

The vaccinia virus used was the Finnish vaccinia strain. In previous experiments we had found that a stock virus, containing at least $10^{7.5}$ egg-infective doses per ml., was capable of causing an apparent infection in the rabbit's eye only when inoculated undiluted. Therefore we again used an undiluted inoculum.

We had some difficulty in finding a strain of herpes-simplex virus which was pathogenic to the rabbit's eye. The first attempts, with two strains recently isolated in primary human amniotic cells from human keratitis, were completely unsuccessful. Thereafter two other strains of herpes virus, also derived from human eyes, were combined, and with an undiluted inoculum of this combined strain a distinct infection was produced consistently in the rabbit.

* Aided by grants from the Sigrid Jusèlius Foundation.

TABLE I—EFFECT OF INTERFERON ON EXPERIMENTAL VACCINIA-VIRUS INFECTION IN RABBITS' EYES

| Day | Part of eye | Rabbit 1 | | Rabbit 2 | | Rabbit 3 | | Rabbit 4 | |
|---|---|---|---|---|---|---|---|---|---|
| | | Interferon | Control | Interferon | Control | Interferon | Control | Interferon | Control |
| 5th | Lids | − | − | − | Ectropion | − | Ectropion | − | Ectropion |
| | Conjunctiva | − | + | − | +++ | − | +++ | ± | +++ |
| | Cornea | − | + | + | +++ | + | +++ | ++ | +++ |
| | Uvea | − | − | − | − | − | ± | − | − |
| 7th | Lids | − | − | − | Ectropion | − | Ectropion | − | Ectropion |
| | Conjunctiva | − | + | − | +++ | + | +++ | + | +++ |
| | Cornea | − | + | + | +++ | + | +++ | + | +++ |
| | Uvea | − | − | − | +++ | − | + | − | +++ |
| 9th | Lids | − | − | Ectropion | Ectropion | − | Ectropion | Ectropion | Ectropion |
| | Conjunctiva | − | − | ++ | + | − | ++ | ++ | +++ |
| | Cornea | − | +(scar) | ++ | + | + | + | +++ | + |
| | Uvea | − | − | ++ | ++ | +++ | +++ | +++ | +++ |
| 14th | Lids | − | − | − | − | − | − | − | − |
| | Conjunctiva | − | − | − | − | − | − | − | − |
| | Cornea | − | +(scar) | ++(scar) | ++(scar) | +(scar) | ++(scar) | +(scar) | ++(scar) |
| | Uvea | − | − | − | − | − | − | − | − |

− =no symptoms.
± to +++ =increasing degrees of symptoms.

Symptoms of infection were
Lids—ectropion.
Conjunctiva—congestion, chemosis, exudate.
Cornea—ulcers, scar.
Uvea—congestion, œdema of iris, turbid aqueous humor.

A superficial scarification was made on the cornea of anæsthetised white rabbits with a trepan, giving a circular lesion of 5 mm. diameter. 0·05 ml. of virus was then instilled on the cornea. Immediately after virus inoculation, about 0·2 ml. of interferon was dropped into the right eye, and 0·2 ml. of the control preparation into the left eye. This application was repeated during the next 4 days, about six times daily. The eyes were then inspected every 2nd day. When lesions had developed, both macroscopic and biomicroscopic examinations were made. Fluorescein staining facilitated the estimation of corneal lesions. For brevity, the right eye will be termed below the interferon eye, and the left eye the control eye.

Interferon alone was instilled as described above on the eyes of two rabbits in order to study the possible toxic effects of interferon.

## Results

No toxic effects could be found in the eyes treated with interferon alone.

Table I shows that the onset of an apparent vaccinia infection was clearly delayed, in the eyes treated with interferon, for 4 days after virus inoculation. Furthermore the disease was milder in the interferon eyes than in the control eyes. In rabbit 1, in which the disease in the control eye was milder than in the other rabbits, the interferon eye remained completely free from infection. The findings in table I also suggest that the superficial parts of the eye were better protected by interferon than the deeper parts. Results similar to those given in table I were also obtained earlier in preliminary experiments with two rabbits.

The herpes-simplex infection (table II) was more rapid and severe than the vaccinia infection. The course of infection varied considerably in individual eyes, but no clear and consistent difference could be observed between interferon eyes and control eyes.

## Discussion

Our results confirm the finding of Isaacs and Westwood (1959) that interferon can inhibit virus growth in vivo without any obvious toxic effects. Our test system would no doubt have been more sensitive to any toxic effects of interferon than that of Isaacs and Westwood, but biomicroscopical examination of interferon-treated eyes did not reveal any toxic changes in the eyes.

The lack of effect of interferon in herpes-simplex infection of rabbits' eyes is in line with earlier findings on the resistance of the herpes virus to interferon on chick chorion (Isaacs et al. 1958) and in tissue cultures (Ho and Enders 1959).

In the hands of Isaacs and Westwood (1959) interferon could "completely" protect the rabbit skin against vaccinia virus, when the dosage and timing were appropriately adjusted. In view of the low concentration of interferon which we used, the application of interferon mainly after the virus, and the large dose of virus inoculum, it is not surprising that we obtained only partial protection of the rabbit's eye against vaccinia virus. On the other hand, one cannot exclude the possibility that the delayed vaccinia infection in the interferon-treated eyes was due to reinfection from the untreated eye of the same rabbit rather than to incomplete effectiveness of interferon.

Slight signs of infection are more easily observed in the eye than in the skin. Attempts are now in progress to suppress vaccinia infection in rabbits' eyes by prolonged treatment with concentrated interferon preparations.

If interferon can be used in man without harm, superficial viral infections of the eye might very well lend themselves to the study of the activity of interferon. Some

TABLE II—EFFECT OF INTERFERON ON EXPERIMENTAL HERPES-SIMPLEX INFECTION IN RABBITS' EYES

| Day | Part of eye | Rabbit 1 | | Rabbit 2 | | Rabbit 3 | | Rabbit 4 | | Rabbit 5 | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Interferon | Control | Interferon | Control | Interferon | Control | Interferon | Control | Interferon | Control |
| 3rd | Conjunctiva | − | + | +++ | + | + | + | + | + | + | + |
| | Cornea | − | + | +++ | ++ | − | ++ | ++ | ++ | +++ | +++ |
| | Uvea | − | + | +++ | + | − | ++ | + | + | + | + |
| 5th | Conjunctiva | + | +++ | +++ | +++ | + | ++ | +++ | +++ | +++ | +++ |
| | Cornea | ± | +++ | +++ | ± | ± | ++ | +++ | +++ | +++ | +++ |
| | Uvea | + | +++ | +++ | − | + | ++ | +++ | +++ | +++ | +++ |
| 12th | Conjunctiva | − | − | Panoph-thalmitis | − | − | − | − | − | Panoph-thalmitis | Panoph-thalmitis |
| | Cornea | + (scar) | ++ (scar) | | ++ (scar) | + (scar) | ++ (scar) | +++ (scar) | ++ (scar) | | |
| | Uvea | − | − | | − | ++ | ++ | ++ | ++ | | |

The symptoms, and their degree, were as shown in table I.

of these diseases still constitute an important and difficult medical problem.


### Summary

The external application of interferon (derived from rabbit-kidney cells) on the eyes of six rabbits for 4 days following corneal inoculation of vaccinia virus, clearly delayed and suppressed the symptoms of infection. The same interferon treatment did not affect the course of herpes-simples infection in the eyes of five rabbits.



REFERENCES

Cantell, K. (1960) *Arch. ges. Virusforsch.* (in the press).
Henle, W., Paucker, K. (1958) *Virology*, **6**, 181.
— Henle, G., Deinhardt, F., Bergs, V. V. (1959) *J. exp. Med.* **110**, 525.
Ho, M., Enders, J. F. (1959) *Virology*, **9**, 446.
Isaacs, A. (1959) *in* Virus Growth and Variation (edited by A. Isaacs and B. W. Lacey); p. 102. London.
— Burke, D. C., Fadeeva, L. (1958) *Brit. J. exp. Path.* **39**, 447.
— Lindenmann, J. (1957) *Proc. roy. Soc.* B. **147**, 258.
— Westwood, M. A. (1959) *Lancet*, ii, 324.
Lindenmann, J., Burke, D. C., Isaacs, A. (1957) *Brit. J. exp. Path.* **38**, 551.
Porterfield, J. S. (1959) *Lancet*, ii, 326.
Wagner, R. R. (1960) *Bact. Rev.* **24**, 151.


## A FATAL CASE OF ECZEMA VACCINATUM


E. O. R. REYNOLDS
M.B., B.Sc. Lond.

HOUSE-PHYSICIAN TO THE CHILDREN'S DEPARTMENT, ST. THOMAS' HOSPITAL, LONDON, S.E.1


ECZEMA vaccinatum, a serious disease in which multiple vaccinial lesions arise on eczematous skin, is rare and should be largely preventable. The following case is presented to draw attention to the continuing occurrence of the disease, although the danger of vaccinating members of eczematous families has been known for half a century (Dock 1906). (The classification of vaccinial complications suggested by Lewis and Johnson [1957] is followed.)

### Case-report

An unvaccinated girl, aged 2 years, of mixed European and West Indian descent, had had infantile eczema since she was 3 months old. This affected the forehead, arms, and legs, and it had been treated with cremor zinci et ung. picis carb. 2%, and hydrocortisone cream 1% for exacerbations.

4 days before the child's admission to hospital a vesicular eruption had appeared on the legs, and had spread to the arms and face. 10 days before this her younger brother had been vaccinated. He had a typical primary reaction on his upper arm, which was uncovered, and he also had slight eczematous lesions of his neck. The parents said that when he was vaccinated no inquiry had been made about a family history of skin disorder. The patient was not known to have been in contact with the herpes-simplex virus, and she had had no other illnesses.

**Fig. 1—Skin lesions at the time of admission to hospital.**

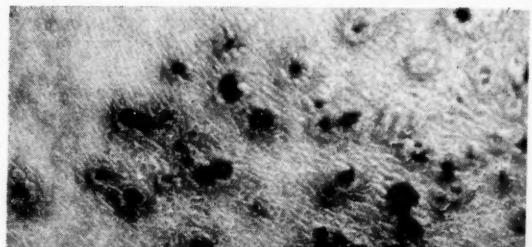


**Fig. 2—Part of the thigh, showing the umbilicated vesicular eruption.**

*Physical Findings*

On admission to hospital the child was ill and slightly dehydrated. Her temperature was 102·6°F, pulse-rate 110 per min., and respirations 30 per min. A severe umbilicated vesicular eruption (fig. 1), with lesions 5–10 mm. in diameter, affected the forehead, eyelids, cheeks, chin, arms (from just below the axillæ downwards but excluding the palms and fingers), and legs (from the groins downwards but sparing the toes and soles). There were a few isolated lesions on the buttocks and abdomen, but none were seen inside the mouth or on the conjunctivæ. This distribution accurately followed that of her eczema. The rash was confluent in many areas (fig. 2), and exuded fluid which was mostly clear, though in some places it was bloodstained. Irritation was intense, and there was secondary infection on the forehead. Small discrete lymph-glands were palpable in both anterior triangles of the neck, but not elsewhere.

A diagnosis of eczema vaccinatum was made.

*Course, Treatment, and Laboratory Findings*

The child was nursed with sterile precautions, the affected areas being exposed. The limbs were tied to a cradle to prevent scratching. Sedatives, antibiotics, and fluids were given at first by mouth, and from the 6th day by intravenous infusion. Antivaccinial gamma-globulin 1 g. was given intramuscularly for 2 days following admission, 0·75 g. was given on the 9th day, and 1 g. on the 11th day. Gamma-globulin and neomycin (1/2%) eyedrops were instilled daily into the conjunctivæ. Chlortetracycline 1/2% cream was applied to the skin.

By the 4th day a few new lesions had appeared, and there was generalised lymphadenopathy and enlargement of the liver.

On the 6th and 9th days the child had episodes of hypothermia to 89·4 and 87·0°F, each lasting several hours. These responded to intravenous hydrocortisone and local heating.

On the 9th day the hæmoglobin was 72% (Haldane), and the blood-urea 10 mg. per 100 ml. Plasma-proteins totalled 5·1 mg. per 100 ml. (albumin 2·7 mg. and globulin 2·4 mg.). The cerebrospinal fluid was normal. By this time the rash was mostly confluent and exuding large quantities of fluid; in many areas the full skin thickness was lost. The child also had intermittent diarrhœa.

On the 10th to 11th days there was a 24-hour period of anuria, during which the blood-urea rose

to 54 mg. per 100 ml. Blood-cultures grew coagulase-positive staphylococci. The child died next day.

*Postmortem Findings*

The skin was as described above. Large fleshy lymph-glands were found in the axillæ, the groins, and the neck. The brain was normal. The lungs were œdematous, with patches of early consolidation. Several freshly ulcerated areas were seen in the stomach, the largest being 2 cm. in diameter and covered with fresh sloughs. There were small patches of inflammation in the postcricoid region of the œsophagus and at its lower end, but no ulceration of the small or large intestine. The liver showed severe fatty changes, and the kidneys were pale and slightly swollen. The spleen and adrenals were normal.

*Postmortem Virology and Bacteriology*

The vaccinia virus, and resistant staphylococci and fæcal streptococci, were isolated from specimens of skin and organs taken post mortem.

## Discussion

Probably the first record of generalised vaccinia (widespread vaccinial lesions on normal skin) is the case described by Conzals in 1810 (Tedder 1936). The patient contracted the disease after sniffing powdered vaccination scabs, cutaneous vaccination having failed. Hutchinson (1879) reported another which appeared after normal vaccination.

The first description of vaccinial lesions appearing on eczematous skin was in 1882 by Martin, who recorded the case of a child with atopic eczema on whose skin widespread vesicles had appeared after the mother and brother had been vaccinated. 5 years later Kaposi (1887) described similar cases, and as a result the clinical syndrome in which umbilicated vesicles are superimposed on skin disease is known as Kaposi's varicelliform eruption. If this eruption appears on atopic eczema and is caused by the herpes-simplex virus it is designated eczema herpeticum, or by the vaccinia virus, eczema vaccinatum (Tedder 1936). Clinically the two are indistinguishable (Lewis and Johnson 1957, Sexton et al. 1957).

In 1906 Dock, reporting Blochmann's work, drew attention to the danger of vaccinating the members of eczematous families, and since then there have been many reports of widespread vaccinial lesions superimposed on atopic eczema (Graves and Dowman 1937, McKhann and Ross 1938, Strickler 1944, Hershey and Smith 1945, Fries et al. 1948, Fasal 1950, Kempe and Benenson 1955, Sexton et al. 1957, Lewis and Johnson 1957, Reynolds and Joos 1958, &c.).

The incidence of generalised vaccinia and eczema vaccinatum is uncertain, since many cases are probably not reported. Until recently the two diseases have not been clearly differentiated, and their combined incidence is probably between 1/50,000 and 1/100,000 vaccinations (Jubb 1943, Reynolds and Joos 1958). In Jubb's large series the case-mortality was 11·7%, or 1·2 deaths per million vaccinated.

The largest recorded series of eczema vaccinatum is that of Fries et al. (1948) who found an incidence of 1/150,000 in the mass vaccinations in New York in 1947. The case-mortality was 4%. Case-mortalities up to 40% have previously been reported (Kempe and Benenson 1955).

Probably two-thirds of all cases of widespread vaccinia have skin disease—mainly atopic eczema (Hershey 1945)—and eczematous subjects run a very much higher risk of contracting cutaneous vaccinial lesions than do those unaffected by skin disorders (Fries et al. 1948). Fries et al. observed sixteen cases of eczema vaccinatum, in one New York hospital, all of which had atopic eczema affecting the limbs, cheeks, and neck. Only one had been vaccinated (3 years previously), and all had been in contact with recently vaccinated people. 70% were under 2 years old.

The disease is usually transmitted by direct contact between skin and virus (Lewis and Johnson 1957). But hæmatogenous spread localising to disordered skin is possible as was shown by Calmette and Guérin (1901), who found that laboratory animals injected intravenously with vesicular fluid developed vesicles on previously scarified skin.

In the absence of skin disease the lesions may be localised to areas of direct contact with the virus (secondary or satellite vaccinia). But, with hæmatogenous spread the typical distribution of the rash (which appears 7–11 days after contact with the virus in 80% of cases) is centripetal, the trunk being affected more than the limbs (Jubb 1943). In the presence of eczema and other skin diseases, however, the lesions are confined almost exclusively to the affected areas (Hershey and Smith 1945, Reynolds and Joos 1958).

## Conclusions

In the case presented here the history of atopic eczema and of contact with a recently vaccinated sibling, the distribution and characteristics of the rash, and the course of the illness, are typical.

The skin of candidates for vaccination should be examined carefully, and no-one with significant skin disorder should normally be vaccinated, though in a smallpox outbreak balanced assessment of the relative risks has to be made. In doing this the area of diseased skin is important; the larger this area the more serious the eczema vaccinatum should it arise.

Before vaccination a careful history should be taken for evidence of skin disorder in the family or immediate environment, and no close contact with those with skin disorders should be allowed for 21 days afterwards (Reynolds and Joos 1958). Reactions should be covered to prevent accidental contamination of others, and it should be made clear that for a vaccination reaction to be left uncovered at least until the scab has separated is dangerous to others. Conversely, those with skin disease should be aware of the danger of contact with the vaccinia virus. Because atopic eczema rarely appears before 3 months of age, the children of families with atopic histories should be vaccinated at 2–3 months (Reynolds et al. 1958), for vaccination at this age has proved effective (Doorschodt 1957).

With the simple precautions described above the case reported here would not have arisen, and the incidence of eczema vaccinatum could be reduced.

I should like to thank Dr. H. J. Wallace and Dr. B. D. R. Wilson for permission to publish this case; Dr. J. E. Cullis for helpful criticism and advice; Dr. Donald Teare for the postmortem examination; the photographic department of St. Thomas' Hospital for the photographs; and Dr. F. O. MacCallum and Dr. J. C. MacDonald of the Virus Reference Laboratory, Colindale, for the postmortem virological and bacteriological studies, and for supplying the hyper-immune gamma-globulin.

REFERENCES

Calmette, A., Guérin, C. (1901) *Ann. Inst. Pasteur*, **15**, 161.
Dock, G. (1906) *N.Y. med. J.* **83**, 11.
Doorschodt, H. J. (1957) *Maandschr. Kindergeneesk.* **25**, 1.
Fasal, P. (1950) *J. Amer. med. Ass.* **144**, 759.
Fries, H. J., Borne, S., Barnes, H. L. (1948) *J. Pediat.* **32**, 532.

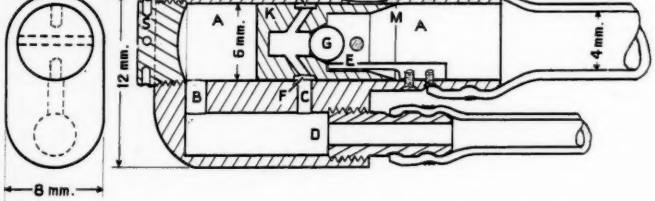
*References continued overleaf*

# New Inventions

## MULTIPLE-RETRIEVING SMALL-INTESTINAL BIOPSY TUBE

SUCTION biopsy of the gastric mucosa, first devised by Wood et al.,[1] has been employed in many centres. More recently the same principle has been used for biopsy of the small-intestinal mucosa. Shiner[2] described an instrument which was essentially the same as the Wood tube but slightly more flexible and longer. Other valuable modifications have been made, particularly the "multipurpose" instrument of Brandborg et al.,[3] the "intestinal biopsy capsule" of Crosby and Kugler,[4] and the tube designed by Henning et al.[5] The last two instruments differ from the Shiner tube in that a wire no longer passes down the tube to operate the knife, and so the flexibility is increased.

To obtain multiple mucosal specimens from different levels of the small intestine, it is essential (1) that the biopsy instrument should be flexible enough to pass along the small intestine; (2) that the instrument should be capable of taking multiple biopsy specimens; and (3) that it should be possible to tell from which level the biopsies came. Although Shiner's tube and the tube described by Henning et al. are capable of taking multiple specimens, these become mixed up within the cutting head, and on withdrawing the instrument the specimens cannot be sorted into their appropriate levels. The Crosby biopsy capsule can be fired only once, having then to be withdrawn, reset, and passed again.




The tube we describe was designed to overcome these defects. It will pass well down the small intestine, taking any number of pieces of mucosa and delivering them to the operator as they are cut, thus revealing the level from which they came.

### THE INSTRUMENT

The cutting head (26 × 12 × 8 mm.) is composed of a cylinder, A, fed by ports B, C, and D (see figure). The cylinder, of 6 mm. internal diameter, contains a lateral hole, L (diameter 2·5 mm.), through which the mucosa is sucked. The bottom end of the cylinder is closed by a capstan screw, S, and the proximal end is attached to a polyvinyl tube of 4 mm. internal diameter and 2 m. long. The port, D, is connected to a radio-opaque polyethylene tube of 1 mm. internal diameter and 2 m. long. The knife, K, is a hollow piston 10 mm. long with a sharp leading edge, M. A narrow channel, F, encircles the knife about midway down its length, and from this channel holes pass obliquely into the interior. Within the knife is a non-return ball valve, G, which allows fluid to pass from the channel, F, into the centre of the knife. The cylinder and the knife are lapped together to a perfect sliding fit. The movement of the knife beyond the lateral hole is arrested by a stop, E.

The two tubes are bound together at 30 cm. intervals. The distal end of the narrow tube is fitted with a Luer adaptor which is then attached to one arm of a standard metal three-way tap; the second arm is connected to a source of negative pressure of 50 cm. Hg, and the third arm to a 100 ml. Luer-lock syringe.

### TECHNIQUE

When a negative pressure is applied to the back of the knife via port B and the narrow-bore tube, the knife is sucked back, thus opening the lateral hole, L, and closing the port, C. With negative pressure still applied to the narrow-bore tube, a lesser negative pressure is applied to the wide-bore tube by means of a 30 ml. syringe. This sucks in a knuckle of mucosa through the lateral hole, L. Via the three-way tap, the negative pressure on the narrow-bore tube is rapidly changed to positive by compressing a 100 ml. syringe filled with fluid. This positive pressure is transmitted down the narrow-bore tube, through the ports D and B and to the back of the knife, which moves rapidly forward cutting off the mucosa sucked through the hole, L. When the knife is fully closed it rests against the stop, E, and, as in the figure, the channel, F, comes opposite the port, C; the fluid passes through C into F, and thence through the small holes into the centre of the knife. The ball valve, G, then opens, allowing the fluid to pass through the knife into the wide-bore cylinder, A, and up the tube. This flushes the specimen of mucosa up the tube and delivers it at the proximal end.

To reset the knife, negative pressure is again applied to the narrow-bore tube, and transmitted through C into the channel, F, and so to the interior of the knife. This closes the ball valve, and allows a negative pressure to be exerted behind the knife. The knife is then sucked backwards to the fully open position closing off the channel, F. That the knife is open can be confirmed by applying a small positive pressure on the wide-bore tube; if the knife is open, no resistance will be felt.

When tested on the bench with freshly removed small intestine or stomach, it can be shown that every time mucosa is sucked into the lateral hole, L, it can be cut off by the knife and delivered at the upper end of the tube. If no specimen is delivered, then no cut has been made. The only exception is that very occasionally the specimen may become stuck in the cutting head. Therefore if, in vivo, no mucosa is delivered, the knife should be opened and quickly closed again, and the tube washed through with a further 100 ml. of fluid, when the specimen will be dislodged and carried up.

The size of the specimen depends on the degree of negative pressure applied. If the pressure is insufficient no mucosa may enter the lateral hole, L. On the other hand if the pressure is too great, there is a theoretical possibility of perforating the intestine. In practice we have found that suction with a 30 ml. syringe produces adequate negative pressure without making the cut too deep.

### RESULTS

The tube has now been used in 36 cases, and in 34 satisfactory biopsy material was obtained from the small intestine. In 32 cases multiple specimens were taken from different levels of the jejunum, duodenum, and stomach, without complications.

The advantages of this tube considerably increase the

1. Wood, I. J., Doig, R. K., Motteram, R., Hughes, A. *Lancet*, 1959, i, 18.
2. Shiner, M. *Gastroenterology*, 1957, **33**, 64.
3. Brandborg, L. L., Rubin, C. E., Quinton, E. W. *ibid.* 1959, **37**, 1.
4. Crosby, W. H., Kugler, H. W. *Amer. J. dig. Dis.* 1957, **2**, 236.
5. Henning, N., Zeitler, B., Neugebauer, I. *Dtsch. med. Wschr.* 1959, **84**, 1961.

### DR. REYNOLDS: REFERENCES—*continued*

Graves, G. W., Dowman, C. (1937) *N.Y. med. J.* **37**, 1833.
Hershey, F. B., Smith, W. E. (1945) *Amer. J. Dis. Child.* **69**, 33.
Hutchinson, J. (1879) *Brit. med. J.* ii, 960.
Jubb, A. A. (1943) *ibid.* i, 91.
Kaposi, M. J. (1887) Pathologie und Therapie der Hautkrankheister. Berlin.
Kempe, C. H., Benenson, A. S. (1955) *Pediat. Clin. N. Amer.* **2**, 19.
Lewis, H. M., Johnson, F. C. (1957) *Arch. Derm.* **75**, 837.
McKhann, C. F., Ross, R. A. (1938) *Pediat. Clin. N. Amer.* **22**, 785.
Martin, H. A. (1882) *J. Amer. med. Ass.* **21**, 393.
Reynolds, A. H., Joos, H. A. (1958) *Pediatrics, Springfield*, **22**, 259.
Sexton, G. B., Labzoffsky, N. A., Ross, W. G. (1957) *Arch. Derm.* **75**, 837.
Strickler, A. (1944) *Urol. cutan. Rev.* **48**, 340.
Tedder, J. W. (1936) *Arch. Derm.* **34**, 1008.

potential value of intestinal biopsy in the study of the morphology and function of the intestinal mucosa.

We are grateful to many friends for help and encouragement. Thanks are especially due to Dr. Ian Wood of the Walter and Eliza Hall Institute, Melbourne; to Prof. A. C. Fraser and Mr. Norman Bates of the department of pharmacology and medical biochemistry Birmingham; and to the manufacturers, Messrs. H. A. Taylor & Son, Melbourne, for their help and skill in making the final instrument.

Wellcome Research Unit, Christian Medical College, Vellore, South India — S. J. BAKER, M.D. Melb.

The Walter and Eliza Hall Institute of Medical Research, Royal Melbourne Hospital, Victoria, Australia — A. HUGHES, B.E.E. Melb., A.M.I.E. Aust.

## A NEW BLADDER SYRINGE

THOSE who use a bladder syringe are well aware of the advantages of an instrument with a glass barrel with a metal plunger. The Riches bladder syringe, the best-known of this kind, has given good service. It has the disadvantage, however, that the barrel may be broken, and when this happens the repair is costly and often takes much time because of the necessity to cement the barrel into the metal mounts. To overcome this disadvantage a bladder syringe has been designed which is basically similar in pattern to the Riches syringe, but has replaceable barrels and pistons (see figure).

A glass barrel, with its own fitting piston, slides between rigid metal side members and rests on carefully fitted rubber washers at the nozzle mount and at the top cap. The syringe is reassembled after sterilisation, and when the top cap is screwed into position a water and airtight fit is achieved.

With reasonable care this syringe has proved as efficient as the original Riches pattern, and it has the following advantages:

1. The initial cost is low.
2. The cost of replacement of barrel and piston is less than that of repairing and recementing a Riches-pattern syringe.
3. The risk of breakage during sterilisation is small, since the barrel is free in its mounting and the differing coefficients of expansion of metal and glass become unimportant.
4. The metal frame helps to protect the barrel from impact fracture.
5. A broken barrel can be replaced immediately from a supply of spares kept in the hospital.

This instrument has now been used for about 6 months at All Saints' Hospital, and has proved very satisfactory. A modicum of care is required in assembly, but otherwise no difficulties have arisen in its use.

The syringe is available from Allen & Hanburys, Ltd., 48, Wigmore Street, London, W.1, from one of whose representatives the idea originated. I should like to thank them for help in the design and manufacture.

All Saints' Hospital, London, S.E.11 — ROBERT COX, M.B.E., M.B. Lond., F.R.C.S.

## A NEW TYPE OF ANGLED-CATCH FORCEPS FOR ANTERIOR COLPORRHAPHY

IN correcting minor degrees of urethrocele and cystocele, or in making the vaginal approach for a sling operation, particularly where there has been a previous anterior colporrhaphy, the anterior vaginal wall has to be opened up under circumstances which can be difficult with the usual straight-catch forceps. These jut out towards the operator, hinder his movements, and are liable to become entangled with catgut, needle-holder, or some other instrument.

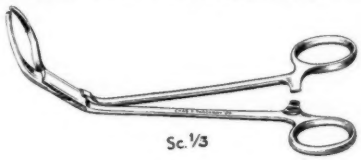



Fig. 1.

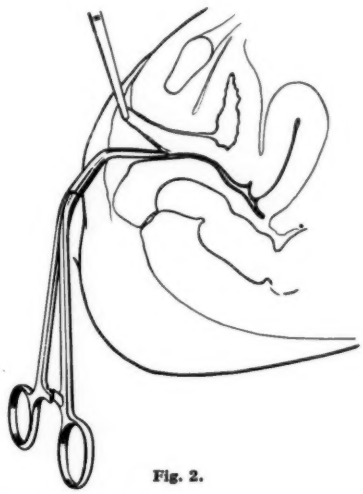


Fig. 2.

To overcome the difficulty and at the same time to give better access to the anterior vaginal wall, a Littlewood's catch forceps has been angled as shown in fig. 1. When in use (fig. 2) the shaft and handle of this forceps lie close against the perineum, offering no obstruction to the operator.

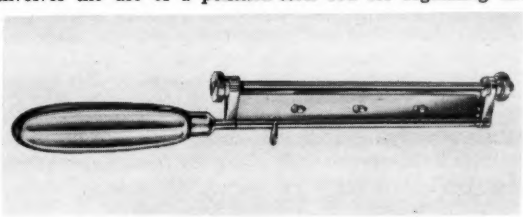
This instrument is made by Charles F. Thackray Ltd., 10, Park Street, Leeds, 1.

Royal Victoria Infirmary, Newcastle upon Tyne, 1 — J. K. RUSSELL, M.D. Aberd., F.R.C.O.G.

## A SKIN-GRAFTING KNIFE

ALTHOUGH conventional hand knives, designed to cut split-thickness skin-grafts at a predetermined depth, have been brought to a high degree of efficiency, they still have tiresome disadvantages. If a rotating roller is used to regulate the depth of cut the graft often tends to adhere to the roller, particularly when very thin skin is taken; an assistant must therefore adjust the skin over the knife blade with forceps, with consequent risk of tearing. Moreover the roller must slide to and fro along its long axis, necessitating slack end-bearings which reduce precision in the setting; hence the graft sometimes becomes gradually thicker as the knife progresses. Usually two adjustments are necessary at either end of the knife to set the depths of cut; if these are set unequally the graft will be thicker at one side than the other.

The knife here described overcomes these difficulties without the need for complex mechanical parts. The principle involves the use of a polished-steel rod for regulating the



depth of cut; this rod has no independent movement, either sliding or rotation, whilst the graft is being taken. At its end-bearings it passes eccentrically through the bushes; hence the depth of cut can be set by rotation of the rod with a single knurled control knob, the rod remaining parallel to the blade at all settings. With this arrangement the bearings can have a precision fit, and there is no " play " in use. Whilst cutting the graft, spontaneous rotation of the rod is slight, but a locking lever is provided to avoid accidental alteration of the setting once it has been made. The knife edge is of the disposable razor-blade type.

This knife is simple to handle, and it will cut thin Thiersch grafts consistently and with precision.

The knife may be obtained from Allen & Hanburys Ltd., 48, Wigmore Street, London, W.1.

Queen Victoria Hospital, East Grinstead, Sussex

JOHN WATSON
M.A., M.B. Cantab., F.R.C.S.E.

## Reviews of Books

### Anatomy: a Regional Study of Human Structure

ERNEST GARDNER, M.D., Wayne State University; DONALD J. GRAY, PH.D., Stanford University; RONAN O'RAHILLY, M.SC., M.D., Wayne State University. Philadelphia and London: W. B. Saunders. 1960. Pp. 999. 105*s*.

ANATOMISTS always find new textbooks interesting, if only because there is widespread dissatisfaction with the ones available. This dissatisfaction springs largely from wide variation in views about what *should* be taught to medical and other students and how. Each teacher seems to have different views; hence the steady stream of new books, few of which receive general acceptance. This new book may, however, be an exception. Though it contains much of the traditional lore, arranged on a regional basis, tediously exact and explicit description of many structures has been avoided. On the other hand, some readers may think that too much " applied " anatomy has been sprinkled through the text, with a garnishing of allusions to embryology, comparative anatomy, and function. But it is this very introduction of non-structural considerations, closely woven into the dead weight of topography, which gives this book its individuality and attraction. The task has been fulfilled with skill, and the result is a readable book, offering the novice a far more lively and balanced aspect of anatomy than is usual.

Apart from the first hundred pages, which give a general introduction to bones, joints, muscles, nervous system, vessels, viscera, skin, development and growth, and radiological anatomy (a superb chapter), the text ambles gently through the body with sufficient references for all but the expert. It is a pity that the central nervous system and embryology were omitted; surely the current view that two other large tomes are needed for these " specialties " is questionable.

The illustrations are all line drawings or diagrams. Their quality varies, but they are many and helpful, and never claim to be a substitute for the dissecting-room. In sum, this is a work which should receive at least a trial in every department.

### Cerebral Dominance and its Relation to Psychological Function

O. L. ZANGWILL, M.A., professor of experimental psychology, University of Cambridge; visiting psychologist, National Hospital, Queen Square, London. Henderson Trust Lecture no. xix. Edinburgh: Oliver & Boyd. 1960. Pp. 31. 10*s*. 6*d*.

IT seems from this very physiological lecture that the link between handedness and cerebral dominance is not at all clear for left-handed people. Professor Zangwill, whose neurological orientation is well known, suggests that the left hemisphere is more often dominant in such people than the right, and that some show imperfect lateralisation. Speech function, too, is less clearly located in these people and recovery from aphasia is more complete: traditional concepts of language localisation only apply, according to Zangwill, in right-handed people of dextral stock. 20 cases of dyslexia studied at Queen Square showed a link with " cerebral ambilaterality " and the suggestion is made that such people have a tendency towards temperamental instability and vulnerability to stress. Professor Zangwill sees cerebral dominance as a graded characteristic, varying in scope from person to person, especially among the left-handed.

### Radiology as a Diagnostic Aid in Clinical Surgery

HOWARD MIDDLEMISS, M.D., F.F.R., D.M.R.D., director of radiology, United Bristol Hospitals. London: Heinemann Medical Books. 1960. Pp. 151. 30*s*.

RADIOLOGY is so much a part of a surgeon's life that few stop to question their own knowledge of it: it is not until the subject is set out in the clear and concise terms which Dr. Middlemiss has achieved that unsuspected gaps are exposed. He has set about the task of enlightening the surgeon either by refreshing his memory or by bringing him up to date in an admirable manner; each diagnostic manœuvre is considered in its application, then method, and finally the findings and their interpretation. The book starts with emergencies, passes to postoperative conditions, and then covers the remaining territory anatomically in six more chapters. The reproductions are first-class as must have been the originals chosen and doubtless created by Dr. Middlemiss himself. This is a sensible book with a kindly word of warning to the surgeon in the last chapter about the effects of irradiation on himself and those around him when, for example, undertaking operative cholangiography. This chapter appropriately includes a note of caution on the patient's behalf—a note which could to advantage have been sounded at the outset and more loudly.

### African Homicide and Suicide

Editor: PAUL BOHANNAN, associate professor, department of anthropology, Northwestern University, Chicago. Princeton, New Jersey: Princeton University Press. London: Oxford University Press. 1960. Pp. 292. 48*s*.

Dr. Bohannan has turned to the neglected subject of comparative criminology to show the effects on the patterns of murder and suicide of tribal customs and social organisation in seven African peoples. In the first chapter, he examines the theories about homicide and suicide, pointing to the relative neglect by sociologists and anthropologists of the study of homicide and comparing this with the concepts of Durkheim, Malinowski, Westermarck, and others on suicide. The next seven chapters consist of essays, based on the official local records, on homicide and suicide among seven African peoples: the Tiv of Central Nigeria, the Basoga, the Gisu and the Nyoro of Uganda, the Luyia and the Joluo of Kenya, and the Alur of north-west Uganda. Dr. Bohannan himself contributes the chapters on the Tiv and the Luyia peoples, and the other chapters were written by other anthropologists. Detailed illustrative cases show the type of homicide or suicide characteristic of each tribe, and those which are unusual.

In a final chapter on the patterns of murder and suicide revealed by the survey, Dr. Bohannan draws attention to the influence of tribal and kinship organisation, belief in witchcraft, and economic factors such as competition for land in determining the commonest type of murder or suicide. Study of the role of killer to victim, or the role in which an individual commits suicide, can throw useful light on the stresses within a community, and Bohannan favours this approach rather than the psychological theories of " motive ". Tables and an appendix summarise the data.

**Advances in Pediatrics** (*Volume XI*. New York: Year Book Publishers. London: Interscience Publishers. 1960. Pp. 285. 68*s*.).—This series has won a reputation for quality in selection, presentation, and production, but this year's selection of subjects is disappointing. Respiration, for instance, has lately been reviewed elsewhere, and the chapters on allergy and aminoacidurias add little new information. But the chapter on the effects of sodium imbalance on the central nervous system is stimulating, and the review of infantile diarrhœa offers new insight into old problems and shows that enthusiasm and ingenuity are still needed in pædiatrics.

# THE LANCET

LONDON 24 SEPTEMBER 1960


## Casualty Departments

THE Nuffield Provincial Hospitals Trust publishes this week a report on Casualty Services and their Setting.[1] This describes a survey of fourteen areas, with twenty main hospitals and several smaller ones, serving a population of some 5 million. The committee [2] sent a clinical team to visit the areas and the casualty departments in them, and their report includes an estimate of how well the various departments fulfilled their own conception of what casualty departments should do; observations on the quality of medical staffing, accommodation, and equipment; and some suggestions on how future assessments of casualty department work could be made. Though brief, it is the most comprehensive examination of this part of the hospital service that has yet appeared in print. Not only the medical but the clerical and secretarial parts of the close-knit team may congratulate themselves on a profound study and a powerful challenge.

On p. 698 we publish the main conclusions and recommendations. The low priority of the subject in schemes of reform is traced mainly to the poor status of casualty work and to the imprecision of the term "casualty". The committee, however, avoid prescribing general remedies, and urge regions to examine their own casualty services and accumulate detailed information before making decisions on the improvements in staffing, organisation, and buildings which will unquestionably be indicated. We could have expected severe criticism of some of our older departments, and we get it. What is more disturbing is the committee's disapproval of some of the departments which have been recently reorganised and rebuilt with the reforms they advocate already in mind:

Conclusion 10 says: "In view of the poor accommodation in the newer departments visited, it is strongly recommended that the functional requirements of casualty departments should be carefully studied in conjunction with all practising personnel, and the results applied in new buildings, as well as in the adaptation of existing accommodation." A comment on a recently opened new department speaks of "first-class medical staff who are providing an enlightened accident service in spite of the drawbacks of planning mistakes and faulty engineering services". Of another department, built three years ago, they remark "the corner of this room is rather a grim sight"; and again, "in 1956 at a cost of £7000 to £8000 an extension was built . . . The design is very poor and has done nothing to enhance the department."

These quotations should, of course, be placed in their proper context, and what the committee approved of in the same departments should be remembered too. But whether everyone will remember it is more than doubtful; for the report is on the bookstalls, and extracts are already in the lay press. Lay, and political, interest in the deficiencies of the casualty services is increasing as rapidly as medical interest, and the suggestion that those who organise these services have already set off in what may be a wrong direction needs attention. Other stimulating topics touched upon include the status and prospects of senior casualty officers; the belief that in any casualty department the services of a consultant should be immediately available throughout the twenty-four hours of the day; the dangers of cross-infection; and contact between casualty departments and rehabilitation and industrial replacement facilities. Among the conditions fundamental to the arrangements for urgent accident and emergency cases is one which we shall all be glad to endorse as soon as we can—"full twenty-four-hour cover by doctors adequately trained for the work they are called upon to do, and who are assured of the stability and importance of this phase of their medical career".

Though the report is entitled "Casualty Services and their Setting", the greater part of it is devoted—and very successfully devoted—to casualty departments themselves. It is true that references are made to industrial medical services, and statements such as "relations between family doctors and this hospital seem uneasy" occur in places. Nevertheless the problems of the cases returned to their own doctor, the impact of one hospital's work on that of its neighbours, the disposal of individual patients in a network of specialties and a multiplicity of hospitals, and the responsibilities of such as the ambulance service in directing unscreened acute cases—all these need much more detailed consideration if a balanced picture of the situation is to be given. They may not form the greater part of the work of casualty departments, but they do provide most of the dilemmas for casualty officers, and a high proportion of the causes of complaint. They would justify an equally extensive survey all to themselves.

We have picked out some of the points which may give rise to surprise and controversy, but they do not reduce our respect for the report, for the committee which prepared it, or for the Trust which inspired and financed it—nor our relief that the "need for leadership and urgent executive action" should now be so firmly pointed out. We are informed that those departments and administrative bodies throughout the country which cooperated did so with special enthusiasm, and that the sympathetic encouragement they were given by the visitors has had a lasting effect. The most charming and most generally appreciated observation was made on the quality of the senior nursing staff: "It was notable that in every hospital the team agreed that the

1. Casualty Services and their Setting: a Study in Medical Care. London: Oxford University Press, for Nuffield Hospitals Trust. 1960. Pp. 135. *7s. 6d.*
2. The steering committee consisted of: Dr. John Fry (chairman), Mr. J. N. Barron, the late Sir Ernest Rock Carling, Mr. Norman Lake, Dr. R. F. L. Logan, Mr. L. W. Plewes, and Mr. Gordon McLachlan (secretary). The surveyors who made the field observations were Mr. Lake, Mr. Barron, Dr. Logan, and Mr. Plewes.

standard of the sister in charge of the casualty department was extremely high. In many cases it would not be an exaggeration to say that the sister was really the lynch-pin of the department." Nothing could be truer than this, and perhaps nothing could be better. But it is definitely not enough.

## Systemic Lupus Erythematosus

SYSTEMIC lupus erythematosus has been known for many years, but its ætiology is still not clear. It is diagnosed more often now because the "L.E.-cell phenomenon" has provided a test which is diagnostic in most cases, and because combinations of steroid and other treatment have offered methods of control. Views on ætiology reflect passing fashions in medicine. Thus at first it was termed "toxic"; then it was ascribed to an infection probably linked with tuberculosis; and latterly it has been grouped with the "collagen diseases". DAMESHEK [1] suggested that systemic lupus erythematosus fitted in better with the immunological diseases. He pointed out that many immune types of disturbance were known to occur in systemic lupus erythematosus, particularly blood disorders such as auto-immune hæmolytic anæmia and thrombocytopenic purpura; in addition, false-positive serological tests for syphilis, and occasionally leucopenia and disturbances of blood coagulation, might be found.

The difficulty with the immune hypothesis has been to explain why autoantibodies develop in an apparently healthy person and why they produce such diverse effects. DAMESHEK [2] has now drawn attention to the rather similar state which develops when bone-marrow "grafts" are inserted into a host whose own immune reactions have been temporarily inactivated by a large dose of radiation. In these circumstances the *host's* antigens stimulate the production of antibodies by the cells in the graft which are still immunologically competent; these autobodies may then attack the cells of the host, and the resulting syndrome has been variously known as runt disease, homologous disease, or secondary disease. Loss of weight, skin disturbances, intractable diarrhœa, grave anæmia, or leucopenia have been found in this disease, and clearly several systems can be affected. How the abnormal cells first arise in the host is unknown, but the possibility that they may cause disease has occurred to several workers. BURNET,[3] for instance, suggests that "forbidden clones" appear in systemic lupus erythematosus.

The idea of abnormal cells gradually involving more systems fits in with our changing ideas on the clinical course of the disease. The standard description of systemic lupus erythematosus is of a rapidly progressive disease of one or two years' duration with fever, skin lesions on the face and often elsewhere, swelling of small joints, splenomegaly, and sometimes hepatic lesions, endocarditis, and finally renal failure. Application of the L.E.-cell test has shown that many patients have a relatively mild illness, surviving for several years during which new symptoms from involvement of previous healthy systems appear from time to time. The difficulty here is to make the diagnosis, since the L.E.-cell test may be negative if the responsible abnormal protein has not developed. But tests for the L.E.-cell phenomenon have been greatly improved and even a finger-prick technique has been devised.[4] According to DUBOIS,[5] of Los Angeles, the test is positive in 80% of cases of systemic lupus erythematosus, though repeated testing over many months may be needed in some cases. False positives arise only in some cases diagnosed as rheumatoid arthritis, and in the long run these may turn out to be cases of lupus. Other tests are not so specific. In the 20% of cases with a negative L.E.-cell test a combination of several clinical signs, such as a discoid lupus rash, involvement of small joints, false-positive syphilis tests, or typical blood-vessel changes in a skin biopsy, is sufficient. DUBOIS states that, in his series of 400 cases, 10% had to be diagnosed on clinical data alone and in another 10% skin biopsy confirmed the diagnosis.

The change of view about the clinical severity of the disease should influence treatment. At present this consists in bed rest and administration of three sets of drugs—salicylates, antimalarial drugs, and steroids. DUBOIS,[5] having reviewed his methods of treating a large group of cases, concludes that the discovery of a few L.E. cells or a false-positive serological test in a patient with none of the recognised symptoms should not be the signal for steroid treatment; no treatment is needed till symptoms appear. If the symptoms are rheumatic—joint swellings with some fever—bed rest and full doses of salicylates are often sufficient. If salicylates fail, or if skin lesions appear, the next line of attack is to give antimalarial drugs. DUBOIS usually chooses hydroxychloroquine ('Plaquenil'), 200 mg. three or four times daily, since no serious side-effects have been reported. He applies steroid therapy only if salicylates and antimalarials fail, or if the patient is critically ill, or if there is neurological or renal involvement. For the relatively mild case he recommends adding a small dose to the combination of salicylates and antimalarial drugs—say, up to 50 mg. cortisone or 10 mg. prednisolone daily. If the symptoms are not controlled, the dose should be raised in steps, by perhaps 20% weekly, and then decreased in the same way when control has been attained. If more than 50 mg. cortisone daily (or the equivalent of the newer steroids) is needed, treatment against the development of peptic ulceration should be given—i.e., six meals a day, antacids, and anticholinergic drugs. With seriously ill patients, steroids in large doses are given from the first; salicylates and antimalarial drugs are not used. A dose of 400 mg. cortisone (100 mg. prednisolone) is a good starting figure, and it can be adjusted up or down as needed; cortisone in doses of up to 4000 mg. daily has been needed to control acute crises. DUBOIS suggests that if steroid treatment has not brought relief in two months, a course of nitrogen-mustard injections should be given.

1. Dameshek, W. *Ann. intern. Med.* 1958, **48**, 707.
2. Dameshek, W. *Arch. intern. Med.* 1960, **106**, 162.
3. Burnet, M. *Brit. med. J.* 1959, ii, 720.
4. Lempert, H., Berlyne, G. M. *ibid.* 1957, i, 1041.
5. Dubois, E. L. *J. Amer. med. Ass.* 1960. **173**, 1633.

The best guides to the control of steroid therapy are the clinical picture and the hæmoglobin level; if the kidneys are involved, tests of renal function should be repeated at intervals. The erythrocyte-sedimentation rate is not helpful since it often remains raised after complete clinical remission, and the L.E.-cell test is too slow to change to be useful for controlling treatment.

DUBOIS has compared the action of several steroids in his cases. 50 patients were treated with dexamethasone and compared with similar groups treated with methylprednisolone, triamcinolone, and prednisolone or prednisone. Dexamethasone is twenty times as powerful as hydrocortisone and eight times as potent as methylprednisolone. It does effectively control systemic lupus erythematosus, but unfortunately it is considerably more liable to produce side-effects than its less active predecessors. For example, œdema occurred in 28% of patients treated with dexamethasone compared with 6% of those on the prednisteroids; 60% developed a cushing-like appearance and 28% hirsuties, compared with 49% and 3% respectively for those on prednisteroids. Triamcinolone produced a curious muscle weakness,[6] but dexamethasone and the other steroids did not cause this symptom. DUBOIS thinks that the improvement in the blood-count was less with dexamethasone than with the others, and he was also troubled with variation of individual response to this drug. He concludes that, for acute attacks, initial treatment with hydrocortisone is best, and for other cases, including those with renal complications, prednisone or prednisolone is still to be preferred.

One of the dangerous complications of systemic lupus erythematosus is the appearance, often acutely, of an auto-immune type of hæmolytic anæmia; various estimates put the incidence at between 3 and 10%. In most patients full doses of prednisolone—say, 100 mg. daily—will control the attack, and the hæmoglobin level can be restored by blood-transfusion. But in some patients steroids are not effective, and then the question of splenectomy arises. WASSERMAN et al.[7] treated 2 such cases by this operation; in 1 the result was fair, but in the other no improvement ensued. SARLES and LEVIN [8] have reported that splenectomy was successful in 3 cases which were not controlled by steroids; eight months later 1 patient was receiving no treatment, and 2 were controlled by moderate doses of steroids. Clearly the operation should be reserved for the few patients who have not responded to other treatment. The scheme of treatment outlined by DUBOIS indicates the importance of not administering steroids too soon in mild cases, and the equal importance of giving really effective doses of steroids at once in acute cases. Owing to the increasing recognition of milder cases, systemic lupus erythematosus can no longer be regarded as a rare disease: in the Los Angeles County General Hospital it is almost as frequent as leukæmia, rheumatic fever, serum sickness, or pernicious anæmia. So most physicians can expect to have to deal with this disease fairly often.

6. See Williams, R. S. *Lancet*, 1959, i, 698.
7. Wasserman, L. R., Stats, D., Schwartz, L., Fudenburg, H. *Amer. J. Med.* 1955, **18**, 961.
8. Sarles, H. E., Levin, W. C. *ibid.* 1959, **26**, 547.

## The Riddle of Tropical Sprue

THE new methods of obtaining fresh tissue from the intestinal tract have opened up a new approach to the physiology of the intestinal cell and disorders of the gut. Using the principles established by WOOD et al.[1] and TOMENIUS [2] for biopsy of the stomach, SHINER [3] followed by CROSBY and KUGLER [4] and RUBIN [5] have each produced instruments with which one to three biopsies may be taken at a time. RUBIN et al.[6] have now devised a method which may take 25–30 biopsies at a session at any place from the ileocæcal valve to the duodenum, and in our present issue Dr. BAKER, of Vellore, and Mr. HUGHES, of Melbourne, describe another valuable instrument, providing serial sections. ASTALDI and STROSSELLI [7] have studied the normal jejunum in great detail, and gradually the normal histological picture of the ileum is also being depicted. Enzymatic and histochemical studies are beginning to reveal something of the complex metabolic processes taking place in the intestinal cell alongside the essential process of absorption. Large numbers of patients with cœliac disease, idiopathic steatorrhœa, and tropical sprue have now been studied, and definite histological changes in the intestinal mucosa have been demonstrated, though the nature, degree, and extent of intestinal involvement cause debate.

MANSON-BAHR [8] has lately pointed to the contrast with the early work on tropical sprue, in which the occasional patient was studied at necropsy after a long and debilitating illness. But among these early observations on the pathology of the intestinal tract there was much that has been found now to be true.

Sprue was first described as a separate entity by MANSON [9] in 1887 in Annam and VAN DER BERG [10] in 1887 in Java. MANSON thought that the small intestine was atrophied, while VAN DER BERG held that gastric catarrh was the essential lesion, and that atrophy of the intestinal walls and the liver was secondary. Changes in the small intestine were noted by THIN,[11] WETHERED,[12] FABER,[13] JUSTI,[14] and BEGG.[15] Consistent findings were shortening of villi and infiltration with round cells and plasma cells, while ulceration of the ileum was common. Thinning and distension of the intestinal wall was often noted, as might now be expected in patients chronically dehydrated and electrolytically depleted. Needless to say, there were two schools of thought—one that the lesions were a principal factor in the disorder and the other that they were the results of postmortem autolysis.

1. Wood, I. J., Doig, R. K., Motteram, R., Hughes, A. *Lancet*, 1949, i, 18.
2. Tomenius, J. *Gastroenterology*, 1950, **15**, 498.
3. Shiner, M. *Lancet*, 1956, i, 17.
4. Crosby, W. H., Kugler, H. W. *Amer. J. dig. Dis.* 1957, **2**, 236.
5. Brandborg, L. L., Rubin, C. E., Quinton, W. E. *Gastroenterology*, 1959, **37**, 1.
6. Flick, A. L., Quinton, W. E., Rubin, E. C. Communication to American Gastroenterological Association, 1960.
7. Astaldi, G., Strosselli, E. *Amer. J. dig. Dis.* 1960, **5**, 175.
8. Manson-Bahr, P. H. *J. trop. Med. Hyg.* 1960, **63**, 49.
9. Manson, P. China Imperial Maritime Customs Medical Report, 1887; p. 33.
10. van der Berg, C. L. Indische Sprue (Aphthæ tropicale). Batavia, 1887.
11. Thin, G. Psilosis or Sprue: its Nature and Treatment. London, 1890.
12. Wethered, F. J. *Trans. path. Soc. Lond.* 1891, **42**, 116.
13. Faber, K. *Arch. Verdaukr.* 1904, **9**, 333.
14. Justi, K. *Beiheft. Arch. Schiffs.-u. Tropenhyg.* 1913, **5**, 394.
15. Begg, C. Sprue: Its Diagnosis and Treatment. Bristol, 1912.

A major contribution was made in 1915 by BAHR [16] who, though he then thought that sprue was probably caused by infection with thrush fungus, pointed out that clinically the disease may take distinct forms according to the portion of the alimentary tract involved. He gave a good description of the changes found in the ileum of two Europeans who had died of tropical sprue in Ceylon:

"The villi are quadrangular in shape and shrunken, the columnar surface epithelium for the most part preserved, but the cells stain badly and the nuclei can with difficulty be distinguished. Chronic inflammatory changes are evident; the capillaries are congested and the interstitial tissue is packed with small round cells and larger cells (leucocytes and plasma cells); the vessels of the submucosa are greatly dilated; there is general fibrosis and the goblet cells at the fundus of Lieberkühn's crypts are distended. There is some evidence that the muscular coats have been affected by the same inflammatory condition."

In 1924 MANSON-BAHR [17] described two further necropsies on adults who had died in temperate climates, concluding that intestinal ulceration was a primary factor in the pathology. In 1929 MACKIE and FAIRLEY,[18] from Bombay, laid stress on the difficulties of assessing the pathological findings when working on postmortem material in hot climates without cold storage. They too described "withering of the villi" and supported MANSON-BAHR's contention that the cause of tropical sprue was to be found in the intestinal tract. In 1932, however, THAYSEN [19] summarised the previous reports and his findings in non-tropical and tropical sprue: "The organs have shown only some insignificant changes and the pathological changes demonstrated are to be taken as secondary phenomena produced by malnutrition, anæmia and perhaps intoxication from the intestinal canal." His opinion carried weight far in excess of the rather inadequate data put forward to support it, and it was generally accepted for twenty-five years. Even FAIRLEY [20] in 1936 retracted somewhat from his earlier publication, and after failure to find "withering of the villi" at necropsies performed in London came to believe that the findings were the result of autolysis. In 1941 MANSON-BAHR [21] defended the hypothesis that abnormalities of the small intestine were the basis for tropical sprue; and now the new techniques have made histological examination easy and have proved the presence of changes. But as so often happens, in answering a few questions they have posed many more. Are the changes the result of infection and are there numerous causes? Are they the same as non-tropical sprue, and are they related to cœliac disease? Are they caused by dietary defects and is there, even in tropical sprue, a constitutional enzymatic defect in the intestinal cell? It is long since Sir PHILIP MANSON-BAHR set himself to answer some of these questions; but even now his "riddle of tropical sprue" remains something of a riddle.

16. Bahr, P. H. A Report on Researches on Sprue in Ceylon. London, 1915.
17. Manson-Bahr, P. H. *Lancet*, 1924, i, 1148.
18. Mackie, F. P., Fairley, N. H. *Indian J. med. Res.* 1929, **16**, 799.
19. Thaysen, T. H. Non-Tropical Sprue. London, 1932.
20. Fairley, N. H. *Trans. R. Soc. trop. Med. Hyg.* 1936, **30**, 9.
21. Manson-Bahr, P. H. *Trop. dis. Bull.* 1941, **38**, 123.

## Purer Food

THIS week's conference and exhibition in London to celebrate the centenary of the first Food and Drink Act points the contrast with the state of affairs only a century ago. It has become difficult to imagine the apathy and ignorance of the general public a hundred years ago regarding the food they ate or the medicine they swallowed, or to conceive of the unscrupulous, deliberate adulteration practised by some traders. Except for sporadic attempts to detect, and devise punishments for, specific instances of adulteration, the sophistication of basic foodstuffs and drugs was accepted as part of the natural order of things, and its ill effects were taken for granted. The first determined effort to make the truth known in this country was made by a German named ACCUM, who came to London in 1793 with some pharmaceutical and chemical knowledge, and finally, with the help of King GEORGE III's apothecary and others, set up a small chemical laboratory and built up a considerable reputation as consultant and lecturer. His greatest interest was in the composition of foods, and his analyses of hundreds of samples of ordinary articles of diet were finally published in 1820 under the title of *A Treatise on Adulteration and Culinary Poisons*. The cover was appropriately decorated with a design of a spider in a web about to devour a fly, surrounded by intertwined serpents with a skull and crossbones on top. Underneath was a quotation from the 2nd Book of Kings: "There is Death in the Pot". In his book ACCUM described some of the iniquitous practices of his time—for instance, the almost universal addition of alum to flour and bread, the reinforcement of beer by ferrous sulphate, and of gin by sulphuric acid, the adulteration of coffee with chicory and of mustard with capsicum, and the use of salts of copper, lead, and arsenic for colouring. The appearance of this book, which ran into four editions in two years, raised a tremendous outcry. Unfortunately for ACCUM, he also published the names and addresses of culprits; and these and others of the same malignant species were able, largely owing to ACCUM's own imprudence, to convict him on a trivial and entirely irrelevant charge of mutilating books belonging to the Royal Institution. As a result, the public lost confidence in what he had written, and by 1824 the national alarm had almost subsided. One or two abortive attempts were made in the next twenty years to revive the memory of ACCUM's work, but eventually it was the founder and first editor of *The Lancet*, THOMAS WAKLEY, who initiated the campaign which ultimately roused a lethargic Government to legislative action.

In 1850 he appointed Dr. A. H. HASSALL, an eminent microscopist, who had already published papers on the detection of chicory in coffee and of impurities in sugar, and Dr. HENRY LETHEBY, a lecturer in chemistry at the London Hospital Medical College, as members of *The Lancet*'s Analytical Sanitary Commission. His proclaimed intention was "to enquire into and report on the quality of solids and fluids consumed by all classes of the public", and he entered the conflict

with a full sense of the responsibility of his undertaking.

The first report on the Commission's activities appeared in *The Lancet* in 1851 and was concerned with coffee. It disclosed, among other things, that of 213 samples bought in London 184 were adulterated. At the end of three months the names and addresses of the merchants implicated were published; a clamorous outcry arose, particularly as some of the accused had bought their supplies in good faith. The reception of the venture by the lay press, led by the *Times* and the *Manchester Guardian*, was cordial. *Punch* published a series of articles in which the malpractices of food dealers were described by such words as "fraudulent", "scoundrel", "rascality", and "swindle". One lively article described the "imps" of the food trade, among them "the grocer-imp, who enriches his chocolate with brick dust and with a morning draught conveys the materials of a vault"; "the baker-imp who grinds his alum to make his bread and selling the staff of life, makes the staff carry a mischievous weapon for the bowels of those who trust to it"; and "the publican-imp whose ale is sharpened with the fiery edges of vitriol".

For four years *The Lancet* continued to publish its articles. HASSALL's analytical methods were far in advance of any previously known, and his extensive use of the microscope brought to light many scandalous practices. The whole of the work was published by HASSALL in 1855 and created a deep impression on the public mind. In fact, the extent of adulteration decreased considerably over this period. The opportunity for energetic action was this time not allowed to slip. *The Lancet* pressed the Government for the appointment of a Select Committee to consider the whole question of food adulteration, and as a direct consequence the first Food and Drink Act in this or any other country was passed in 1860.

The Act was certainly far from perfect. It permitted, but did not compel, the appointment of official analysts by local authorities; and owing, on the one hand, to the tendency of human beings to do no more than they must, and, on the other, to the fact that many local councils were largely composed of the very people condemned by the wording of the Act, it was administered in such a half-hearted way as to be practically a dead letter. It was asserted, for example, that only some six or seven analysts were appointed, of whom four were allowed to do nothing and two others received at first a few samples, dwindling to extinction by inertia. The only analyst who insisted on his rights was Dr. CAMERON of Dublin, who in 1862 examined 2600 samples of food and drugs, proved 1500 to be adulterated, and secured 342 convictions. In the same year only 300 samples were examined in the whole of England and Wales. In 1872 the provisions of the 1860 Act were extended to drugs, which were undeniably in need of the same protection as foods, and a tentative if somewhat naïve attempt was made to control labelling as well as actual sales. Difficulties in the working of this Act and its obvious shortcomings led finally to the Act of 1875, which, although subsequently amended, extended, and supplemented many times up to 1955, is still the basis on which rests all the communal efforts in nearly all civilised countries to secure that food shall be safe. Today we can only look back in wonder on the time when it was possible for a confectioner to escape with a fine of sixpence for colouring his cakes with lead chromate.

## Annotations

### ANTI-HISTAMINES AND PROTECTION AGAINST LIVER INJURY

THE complex mechanisms underlying the integrity of living cells can no doubt be disturbed in many ways; but the disturbance may commonly be at the same vulnerable point. Judah et al.[1 2] have drawn attention to this important possibility, and have produced strong evidence that this common vulnerable point is the mitochondrial membrane and that measures to reduce its permeability may afford protection against widely diverse injurious agents.

These workers showed in 1956 [2] that the action of several liver poisons—for example, carbon tetrachloride—is associated with mitochondrial swelling and loss of enzymes into the suspending fluid; and further work with the liver carcinogen, thioacetamide, indicated the important damaging role of calcium ions.[3] This work with thioacetamide has been restudied by Judah.[1] In liver slices he estimated the increase of mitochondrial membrane permeability by the amount of malic dehydrogenase that appeared in the supernatant fluid. He has thereby confirmed the importance of the part played by calcium ions, and has obtained convincing evidence of the action of anti-histamines in inhibiting the increased permeability and the associated swelling of the mitochondria. Since thioacetamide does not cause swelling of isolated mitochondria, he suggests that the mitochondrial changes observed with liver slices represent part of the final common pathway of liver-cell damage.

The observations by Judah et al. have now been extended to a form of hepatic damage produced by a virus.[4] Using Gledhill's murine hepatitis virus $MHV_3$, they obtained significant protection of mice by means of the anti-histamine, diphenhydramine hydrochloride. Mice were infected with an L.D.$_{50}$ of the virus, and the treated group received a daily dose of 100 mg. diphenhydramine hydrochloride per kg. body-weight. The survival-rates of the controls after 5, 6, and 7 days were 50, 31, and 16% respectively, while the corresponding figures for the treated animals were 79, 62, and 43%. Evidence of protection was obtained also from histological study of the liver. By the 3rd day after infection diffuse zonal necrosis was found in both groups of animals; but by the 5th day, whereas in the control animals these had become largely confluent and massive, in the treated animals they remained discretely zonal. This was not the only evidence of the protective effect of the anti-histamine; for in the treated animals the serum level of malic dehydrogenase rose much less than in the untreated.

The concentration of virus in the liver was determined on the 4th day by intraperitoneal inoculation of serial

1. Judah, J. D. *Nature, Lond.* 1960, **185**, 390.
2. Gallagher, C. H., Gupta, D. N., Judah, J. D., Rees, K. R. *J. Path. Bact.* 1956, **72**, 193.
3. Dawkins, M. J. R., Judah, J. D., Rees, K. R. *ibid.* 1959, **77**, 257.
4. Judah, J. D., Bjotvedt, G., Vainio, T. *Nature, Lond.* 1960, **187**, 507.

dilutions of liver suspension into other mice. Substantially the same concentration of virus was found in the control animals and in those treated with diphenhydramine hydrochloride. This observation is important, since it is in keeping with the hypothesis that the protection of the liver cells against necrosis was due not to any inhibitory action on the virus but to an action on the metabolism of the affected cells that protects against the effects of viral proliferation.

The lack at present of any specific treatment of viral hepatitis in man will no doubt prompt an early trial of the anti-histamines in this condition. Serial study of liver-cell enzymes in the serum of patients treated in this way should prove a useful method of assessing the results quantitatively. McLean's [5] observations on the protective effect of anti-histamines against some of the hepatic effects of nutritional deficiency suggest that these drugs may be especially valuable in the treatment of the severe forms of hepatitis in malnourished patients.

## BRUCELLOSIS IN BRITAIN

IN this country undulant fever, due to infection with *Brucella abortus*, arises from drinking infected milk or from contact with cattle, 15–20% of which were believed to be infected ten years ago.[6] Some protection is afforded by vaccination [7 8]; but complete prevention depends on eliminating the infection from cattle—a step which is also economically important. A campaign against the disease in man and cattle was launched by W.H.O. in 1951 [9]; and some countries, including much of Scandinavia, have almost entirely rid themselves of this infection.[10] In Britain the public health committee of the British Medical Association have recommended that the disease should be made notifiable.[11]

Following the discovery of cases of brucellosis associated with the drinking of tuberculin-tested (T.T.) milk, doctors and veterinarians in the Oxford region formed a working group to study the incidence of the infection.[12] So far only some of the results [13 14] of these surveys have been published. Meanwhile a retrospective analysis based on hospital records over the past twenty years has revealed some interesting facts.[12]

The recorded hospital incidence of undulant fever has remained fairly steady over the whole period, even though the number of people drinking unpasteurised milk must have fallen considerably. Apparently a higher proportion of cases are being diagnosed correctly: there is some evidence of such a trend elsewhere in England and Wales.[15–17] Perhaps the most startling finding is that of the last 17 cases 7 were in children, of whom 4 were judged to have been infected from raw T.T. milk and 3 from raw undesignated milk; in addition, 5 adults had been infected from T.T. milk. Many members of the public regard T.T. milk as "safe" [12 15]; but this is a misapprehension, and samples from 5% of T.T. herds were found to give a positive biological test when injected into guineapigs.

It is regrettable that a disease commonly due to infected milk is not notifiable, and that existing legislation apparently does not enable the sale of cows yielding such infected milk to be prevented.[7] Other countries have shown that prevention is feasible. In the United Kingdom action is overdue.

## BIOPSY OF THE PROSTATE

MALIGNANT disease of the prostate seldom gives rise to symptoms until the growth has extended beyond the scope of radical operation. In some instances, however, the chance finding of a suspicious nodule or area of induration on rectal examination may lead to further investigation before the opportunity for curative surgery is lost. At this stage the serum-acid-phosphatase value is unlikely to be conspicuously raised, and radiographic examination will only help to exclude secondary spread. Confirmation of the diagnosis must, therefore, depend either on biopsy or on examination of expressed prostatic fluid for exfoliated cancer cells. With this latter procedure the findings are often difficult to interpret, and the results can be relied on only when an expert cytologist makes the examination. For this reason biopsy may be resorted to, particularly as a prelude to radical surgery or when for other purposes definite proof of malignancy is needed.

Needle biopsy by the perineal route has proved both accurate and safe in the hands of some, including Parry and Finelli,[1] who report a series of 66 consecutive biopsies on suspicious prostatic nodules using the Vim-Silverman needle (or its Franklin modification). Most of the specimens were obtained under local anæsthesia, and no complications were recorded. Suitable material for microscopy was obtained in all but 6. The cases were segregated before biopsy into three groups according to whether cancer was regarded as strongly probable, probable, or merely suspected on clinical grounds. In the first group microscopic evidence of cancer was obtained in 18 out of 21 patients (86%), in the intermediate group in 10 out of 24 (42%), and in the improbable group in 3 out of 15 (20%). Thus the results of clinical assessment accorded to some extent with those of biopsy evaluation; and the findings tend to support the view that in about 50% of cases a suspicious prostatic nodule will prove to be at least potentially malignant.

Nevertheless the place of biopsy in suspected prostatic cancer needs to be considered further. In experienced hands diagnostic material may be secured in a high proportion of cases without undue difficulty; but it is all too easy to obtain unrepresentative tissue at the cost to the patient of some discomfort and occasional risk. Admittedly the danger of disseminating the disease by "blind" interference with the neoplasm has been exaggerated—a fact underlined by the frequency with which perurethral prostatic resection is carried out without promoting rapid metastatic spread. But the real risk of prostatic biopsy in suspicious early lesions lies in the interpretation placed on a "positive" result. As is now well known, with advancing age isolated foci of latent cancer in the prostate become increasingly prevalent. Many of these never progress to activity, and in the elderly symptom-free patient they are often best disregarded. In younger patients, however, the question of surgical treatment (as opposed to endocrine therapy) may arise, and it is in such cases that the action which should follow a positive biopsy finding is least clearly agreed. But it is now widely accepted that,

5. McLean, A. E. M. *ibid.* 1960, **185**, 936.
6. Dalrymple-Champneys, W. *Lancet*, 1950, i, 429.
7. Elberg, S. *in* Bacterial and Mycotic Infections of Man (edited by R. J. Dubos). London.
8. *Tech. Rep. Wld Hlth Org.* 1958, no. 148. See *Lancet*, 1958, ii, 273.
9. *Tech. Rep. Wld Hlth Org.* 1951, no. 37.
10. Thomsen, A. *Danish med. Bull.* 1956, **2**, 65.
11. *Brit. med. J.* 1959, i, suppl. p. 71.
12. Bothwell, P. W. *Med. Offr*, 1960, **103**, 85.
13. McDiarmid, A. *Vet. Rec.* 1960, **72**, 423.
14. Bothwell, P. W. *ibid.* p. 425.
15. Barrett, G. M., Rickards, A. G. *Quart. J. Med.* 1952, **22**, 23.
16. Davies, J. E. *Brit. med. J.* 1957, ii, 1082.
17. Wallis, H. R. E. *ibid.* 1957, i, 617.

1. Parry, W. L., Finelli, J. F. *N.Y. St. J. Med.* 1960, **60**, 1766

where the diagnosis cannot definitely be established by other means, biopsy is desirable before endocrine therapy is instituted and obligatory if radical operation is contemplated. Disappointingly, in the series reported by Parry and Finelli, only 6 of the 31 patients in whom the presence of a cancerous nodule was proved were deemed suitable for an attempt at curative surgery.

## SOYA-BEAN GOITRE IN INFANTS

In the United States, many infants who are supposedly intolerant of milk have been reared on soya-bean preparations. In a few of them goitre has developed, often with indications of mild hypothyroidism as well. Rawson and Rall [1] described the first example; another was studied by Van Wyk et al.[2] who had heard of 8 other possible cases; and now 3 more have been recorded in detail by Shepard et al.[3] The goitre disappeared rapidly in Van Wyk's case and in 2 of Shepard's cases when the diet was changed from the soya-bean preparation to milk. In the 3rd patient studied by Shepard the goitre vanished when iodide was given, but unfortunately the soya-bean preparation was also changed at the same time.

McCarrison [4] first showed that soya-bean flour can cause goitre in rats; his findings have been amply confirmed.[5–7] The commercial preparation actually consumed by Van Wyk's and Shepard's infants was shown in the laboratories of the manufacturer to be goitrogenic to rats.[8] Goitres were preventable by iodide supplements, and these have now been incorporated in the formula. Another soya-bean preparation for infant feeding, made by a different firm, is apparently not goitrogenic even when not supplemented with extra iodide.[9]

The mechanism of soya-bean goitre in laboratory animals is not clear. No goitrogen has so far been identified. Van Middlesworth [10] has suggested that soya-bean flour (like cellulose) tends to prevent the reabsorption of thyroxine reaching the gut through the bile. The amount of thyroxine a rat might lose in this way would probably be quite considerable, since the relative bulk of fæces is large in this species. The loss of thyroxine would demand a compensatory increase in the activity of the thyroid, probably with an increase in the size of the gland. The iodine contained in the fæcal thyroxine might or might not be lost to the rat, according to whether or not it was split off by microorganisms in the gut, and reabsorbed as iodide. Hence the rat's thyroid might have to respond to an increased demand for thyroxine with a simultaneous deficit of iodine. The combination would be highly goitrogenic.

It is not very likely that this ingenious hypothesis applies to human soya-bean goitre, since the fæcal excretion of thyroxine is relatively unimportant in man (it seems to be related to fæcal volume, which is relatively small in the human species [11]). The mechanism of soya-bean goitre in man therefore remains unexplained, although it seems likely to be iodide-dependent. The condition does not seem to have been encountered so far in this country, probably because pædiatricians here are reluctant to diagnose milk allergy and hence soya-bean diets are seldom prescribed. But where such diets are prescribed the clinician should remember the possibility of a goitre developing.

Probably no adults consume soya-bean products in sufficient quantity to cause goitre. Van Wyk et al.[2] showed that the soya-bean preparation which caused goitre in infants did not affect radioiodine uptake in adults (though in 2 out of 14 subjects the amount of labelled organic iodine appearing in the plasma was decreased). It is interesting to recall Iversen's [12] tentative suggestion that the cessation of imports of soya-bean into Denmark might have had some share in causing the remarkable epidemic of thyrotoxicosis in that country during the 1939–45 war. He suggested that soya-bean products (used in the manufacture of margarine and cattle cake) might in normal times exercise a restraining influence on thyroid function. This highly ingenious hypothesis seems improbable for various reasons, one of which is that the goitrogenic activity of the soya-bean is unlikely to survive the processes of manufacture, at least in the case of margarine.[5 7]

## IATROGENIC SODIUM RETENTION

Sodium retention is a well-known complication of treatment with some drugs. The most important of these is cortisone; but in long-continued treatment cortisone has now been replaced by prednisone and dexamethasone, with which sodium retention is more unusual. This complication—presenting with hypertension, pulmonary œdema, or congestive heart-failure—may also follow administration of œstrogens, particularly in old men with myocardial disease who are receiving large doses on account of carcinoma of the prostate; but it may also arise during the (doubtfully effective) treatment of coronary-artery atheroma with œstrogens.[13] Phenylbutazone and reserpine are other drugs that may cause sodium and water retention.

Thoughtlessly or unwittingly, medicines containing sodium may be prescribed for patients on low-salt regimes. Rimer and Frankland [14] describe two cases in which fluid retention was increased owing to sodium in an antacid mixture. Their analysis showed that some common antacids contain important amounts of sodium. 'Aludrox', for instance, was found to contain 33 mg. sodium per oz., and 'Gelusil' 5·3 mg. per tablet. Other common medicines, such as mist. gent. alk., mist. kaolin. et morph., and 'Eno Fruit Salt', also contain sodium. And the Brompton hot water mixture (mist. sod. chlorid. co., *N.F.*), which is sometimes given to bronchitic patients in heart-failure, contains 260 mg. sodium in each $^1/_2$ oz. dose.

The dangers of sodium-salicylate treatment in rheumatic fever, especially if the patient is also receiving large doses of cortisone, are increasingly recognised. Pulmonary œdema from this cause was described by Phear [15]; and sodium salicylate should be replaced by aspirin if heart-failure develops or if there is rapid weight gain.[16]

All this we may know but do not always remember as we scribble our prescriptions.


1. Rawson, R. W., Rall, J. E. *Rec. Progr. Horm. Res.* 1955, **11**, 257.
2. Van Wyk, J. J., Arnold, M. B., Wynn, J., Pepper, F. *Pediatrics*, 1959, **24**, 752.
3. Shepard, T. H., Pyne, G. E., Kirschvink, J. F., McLean, M. *New Engl. J. Med.* 1960, **262**, 1099.
4. McCarrison, R. *Indian J. med. Res.* 1933, **21**, 179.
5. Sharpless, G. R., Pearsons, J., Prato, G. S. *J. Nutr.* 1939, **17**, 545.
6. Wilgus, H. S., Gassner, F. X., Patton, A. R., Gustavson, R. G. *ibid.* 1941, **22**, 43.
7. Halverson, A. W., Zepplin, M., Hart, E. B. *ibid.* 1949, **38**, 115.
8. Anderson, D. W., Howard, H. W. *Pediatrics*, 1959, **24**, 854.
9. Sarett, H. P. *ibid.* 855.
10. Van Middlesworth, L. *Endocrinology*, 1957, **61**, 570.
11. Pitt-Rivers R., Tata, J. R. The Thyroid Hormones. London, 1959.
12. Iversen, K. Temporary Rise in the Frequency of Thyrotoxicosis in Denmark 1941–1945. Copenhagen, 1948.
13. Thorn, G. W., Nelson, K. R., Thorn, D. W. *Endocrinology*, 1938, **22**, 155.
14. Rimer, D. G., Frankland, M. *J. Amer. med. Ass.* 1960, **173**, 995.
15. Phear, D. N. *Arch. Middx Hosp.* 1955, **5**, 172.
16. Holt, K. S., Illingworth, R. S., Lorber, J., Rendle-Short, J., Gibson, W. M. *Lancet*, 1954, ii, 1144.

## Special Articles

# FIXED COSTS IN THE HEALTH SERVICE

J. R. SEALE *
M.A., M.D. Cantab., M.R.C.P.
LATELY GOODWIN TRAVELLING FELLOW OF ST. JOHN'S COLLEGE, CAMBRIDGE, AT HARVARD GRADUATE SCHOOL OF BUSINESS ADMINISTRATION

IN earlier papers I pointed out that the percentage of national income spent on medical care in the United States and in Britain has tended to remain constant over a number of years.[1] I further suggested that future expenditure on the health service in Britain could be predicted on the assumption that for the next few years this proportion is unlikely to change greatly. In making this prediction I discounted possible changes in the use of the service as irrelevant.

The purpose of this paper is to show that the use of the the health service does not determine its cost. It will do this by considering the distinction between fixed and variable costs.

### COSTS IN INDUSTRY

A " fixed " cost is an expense which is incurred independently of the quantity of goods sold or produced, or the number of services rendered. A " variable " cost is an expense which varies more or less directly with the volume of production. The difference can be illustrated by examples drawn from industry.

In *retail distribution* most costs are variable.

A retailer buys refrigerators from a wholesaler or manufacturer; their total cost to him varies directly with the number sold. He also has to pay rent, rates, heating, lighting, insurance, and the salaries of salesmen, secretaries, and cleaners. These costs, which are often called overheads, are fixed and remain the same whether he sells one, two, three, or four refrigerators. Fig. 1 shows the relation of total costs to quantity of goods sold in a distributive organisation.

* Now senior medical registrar, St. Mary's Hospital, London, W.2, and the West Middlesex Hospital, Isleworth.

1. Seale, J. R. *Lancet*, 1959, ii, 555: *ibid.* 1960, i, 1399.

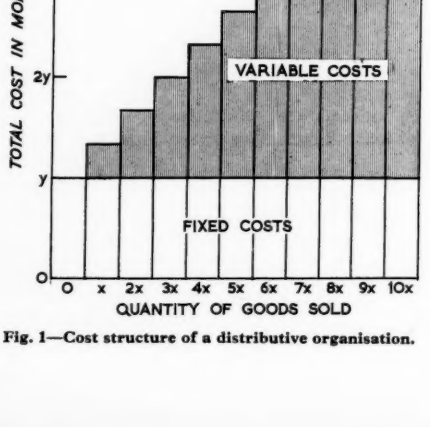



**Fig. 1—Cost structure of a distributive organisation.**

In *manufacturing industries* also, many of the costs are variable.

In a factory making refrigerators the cost of the castings and sheet-metal from which finished parts are made, and of component parts bought from other firms, varies with the number of machines produced. The cost of the direct labour used, such as the machine-tool operators and the assembly-line workers, may be considered variable on the assumption that the wages for unit work remain the same whatever the volume of production. This assumption is reasonable if the workers can either be hired or fired as production varies,† or can be immediately transferred to, or from, other productive work within the plant. In addition, as with retail distribution, there are also fixed costs or overheads which are largely independent of the number of refrigerators produced—that is whether the factory is producing at full or half capacity.

In most *service industries*, however, nearly all costs are fixed. The existence of the service, not the use of it, determines its cost.

The cost of running an express train a hundred miles is about the same whether there is 1 passenger in it or 1000; the cost of

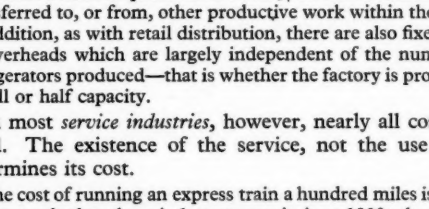



**Fig. 2—Cost structure of a service organisation.**

flying an aeroplane across the Atlantic empty or full of passengers is much the same; the cost of a town fire-brigade in a year when there are no fires and in a year when there are several is much the same; the cost of showing a film in a cinema containing an audience of 2 or of 2000 is almost exactly the same. The cost structure of a service industry is shown in fig. 2.

### FIXED HEALTH SERVICE COSTS

In the health service most of the costs are fixed, and only a few are variable.

The cost of the *general practitioner* service is almost entirely fixed. The doctor is paid a fee per patient per year, irrespective of the number of visits made, patients seen, or time worked. Thus, if in a single month there are widespread epidemics of influenza, measles, and gastroenteritis, the doctors will work long hours and see many more patients than usual, but the total expenditure on general practitioners will remain almost constant. In a fine summer month free of epidemics, the number of services rendered may fall substantially, but expenditure is little less.

The expenditure on *hospitals* accounts for about 60% of all health service expenditure. Over 80% of hospital current

† The assumption that all direct labour costs in industry are variable is less reasonable today than it was before the second world war. With guaranteed minimum wages (e.g., for British dock-workers and American automobile-workers) and redundancy compensation agreements (e.g., for Lancashire cotton-mill operatives and Welsh coalminers), the wages paid to many industrial workers no longer fall immediately production falls. Also, in a period of full employment, management often does not lay off workers as soon as demand for a product falls, lest it finds itself unable to recruit workers again when demand next rises. The effect of such developments is to increase the proportion of costs which are fixed in these industries.

expenditure, and all capital expenditure, represent fixed costs. The salaries and wages of nurses, doctors, laboratory technicians, physiotherapists, radiographers, administrators, secretaries, porters, engineers, cooks, and wardmaids, and the cost of heating, lighting, and maintenance, are the same whether the hospital is full or half-empty. The cost of food, drugs, laboratory and radiographic materials, and so on represent less than 20% of the cost of running the hospitals, and these are the only costs which are reduced if a hospital is partly empty.

In the *local health authority* services, costs are largely unrelated to use. The costs of the district nurses and midwives, the health visitors, the maternity and child-welfare clinics, and even the ambulance service are mostly fixed.

This description of costs in the health service is oversimplified. The use of a service can gradually alter its cost by affecting the fixed costs. If in an individual hospital the number of patients using it falls dramatically and persistently, as has happened in fever hospitals and is happening in tuberculosis and children's hospitals in all the prosperous nations, then the number of staff employed may be decreased, thus lowering the fixed costs. A ward, a wing, a whole hospital, may be closed. But the closing of a ward does not necessarily decrease fixed costs. It may be an opportunity to allow the hospital staff to work shorter hours or to earn more,‡ or to give the patients in the remaining wards more care. Nor does the closing of an entire hospital necessarily have any effect on the national expenditure. If the redundant employees from a closed fever hospital transfer to a new geriatric hospital, or to other hospitals to provide a better service, or to a home-care service, then total expenditure on the service may remain unaltered.

Conversely, if there is persistent pressure for patients to be admitted to a hospital where the bed-occupancy rate is already nearly 100%, then a new ward or a new hospital may be built. This would lead to a large capital expenditure and increased fixed costs. But this pressure, though a necessary cause, is not alone enough to bring this about. Men, materials, and money must be available and the will to use them for this purpose. Without them the new hospital will not materialise, and there will be no increase in fixed costs.

## VARIABLE HEALTH SERVICE COSTS

The costs of the *ophthalmic, dental, and pharmaceutical services* appear at first sight to be variable, because payment depends on items of service rendered or goods supplied. If an optician doubles the number of spectacles he supplies, his payments are doubled; if a dentist extracts half as many teeth, his payments are halved; if a general practitioner increases the dose of prednisolone for his patient from 10 mg. to 20 mg. daily, expenditure on this drug is doubled. These three services combined have in recent years represented barely 20% of expenditure on the health service.

But though the costs of the *ophthalmic and dental services* are indeed almost all variable at the level of the individual optician or dentist, it would be a mistake to conclude that they are 100% variable at a national level. They primarily represent the incomes of dentists and opticians, and large changes in the use of the services they provide would lead to large changes in their incomes if unit payments remained constant. This happened in the early months of the health service, when the incomes of most dentists and opticians rose substantially. But piece-work rates in any organisation are set not at an arbitrary level but at a level which will allow a reasonable income. Thus a large rise in the number of services rendered, causing steeply rising incomes, tends to a cut in the fee paid per item of service. This happened in 1949 and 1950 to the fees paid to dentists and opticians. Similarly a fall in the number of services will tend to a rise in individual fees. These tendencies are well illustrated by the Royal Commission's recommendation that arrangements should be made to ensure that the average annual income of dentists from health-service fees should be £2500 net.

‡ In practice this does not happen in the N.H.S., because rates of pay of hospital staff are determined centrally by the Ministry of Health and not by individual hospitals. It could happen, however, in a health service where financial control was decentralised.

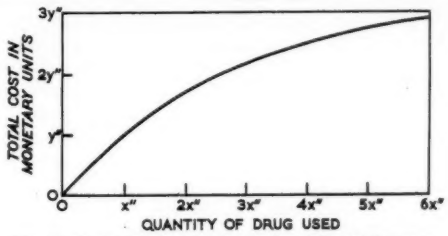



**Fig. 3—Cost of a drug to the National Health Service.**

In the *pharmaceutical service* similar tendencies are present. When a new drug such as penicillin, streptomycin, or cortisone is introduced, unit cost is initially very high. With mass production and mass consumption expenditure would become astronomical if costs of such drugs to the health service were 100% variable. But they are not; for, with quantity production, unit cost to the manufacturer falls and consequently unit price to the National Health Service also falls. Thus though total expenditure on a drug rises with increasing use, it does not do so proportionately (fig. 3); for in the drug industry, as in the health service, most costs are fixed.

## DISCUSSION

Since so many health-service costs are clearly fixed, would it not be reasonable to assume that, at a national level, virtually all costs in the National Health Service—or indeed in any form of health service—are fixed? This would imply that the cost structure of the whole service could be represented by fig. 2 with the variable costs excluded. Changes in the use of the service would not in practice affect significantly its total cost, and could be ignored when budgeting for the future. This is not to say that how the health service is used is irrelevant, for its use is the reason for its existence; it does say, however, that factors other than its use determine its cost. To understand what these are we must look at the fixed costs.

The fixed costs primarily represent the incomes of those employed, directly or indirectly, by the service. If the proportion of the working population whose incomes are derived from providing medical care remains constant, and if their incomes, relative to the incomes of the rest of the nation, do not change, then the proportion of national income spent on medical care will remain constant. Observations made in many countries show that this latter proportion does in fact tend to remain constant over several years.[2]

If there are factors which tend to increase the proportion of the working population providing medical care, then the proportion of national income spent on medical care will tend to rise. This happens during national economic depressions when many workers in the manufacturing, building, and mining industries lose their jobs,

2. International Labour Office. Cost of Medical Care; p. 152. Geneva, 1959.

and consequently much of their income, while those providing medical care keep their jobs. It also seems to happen very gradually as real per-caput national income rises.[3] This gradual and apparently automatic shift of people into occupations such as nursing, medicine, and dentistry, which occurs as a nation becomes increasingly prosperous, can of course be accelerated or retarded by social policy.

Thus a consideration of the nature of fixed costs, and observation of actual expenditure by nations on medical care, both lead to the conclusion that, when predicting national expenditure on medical care, or when budgeting for expenditure on the National Health Service, changes in the use of the service can be ignored, as they do not significantly affect total cost.

I wish to thank Dr. N. F. Coghill for his helpful comments on this paper.

## CASUALTY SERVICES

THE report on casualty services issued by the Nuffield Provincial Hospitals Trust, which is reviewed in a leading article this week, includes the following recommendations:

1. The study established that there is a need for leadership and urgent executive action on the part of hospital authorities to review, reorganise and improve the service for casualties. The medical staffing of such services demands special attention, particularly the provision of adequate consultant cover and the supply, supervision and training of junior staff.

2. The history of casualty services records justifiable public dissatisfaction about their adequacy and also widespread apathy on the part of hospital authorities to correct faults. This has been due to the low priority of the subject in schemes of reform, and this in turn seems to arise mainly from: (*a*) the poor status of casualty work, and (*b*) the imprecision of the term "casualty". Casualty departments tend to embrace a wide range of categories of cases seeking attention and treatment. Because of the increasing number of accidents the most urgent need is to improve the service for those casualties requiring immediate attention and treatment—i.e. "urgent emergency and accident cases".

3. There is therefore a need for an immediate review of the services which hospitals seek to provide in their "casualty" departments and a classification of all hospitals to denote their facilities for the reception of "urgent accident and emergency" cases. Such a review should examine relevant local issues such as the "open door" policy and all the arrangements for medical care. It should also include an evaluation of the function of the casualty department as a source of special teaching material.

4. From the start the horizons of the surveyors were forced well beyond those of the individual hospitals visited. The study showed that if adequate staffing and facilities were to be provided it would be necessary to concentrate services. The organisation for casualties should be based on well-defined catchment areas and should be planned to take account of all the services for medical care already available there. Such organisation will almost certainly entail the rationalisation of present services to ensure immediate diagnosis and effective treatment for those in urgent need of it. It will call for the fullest cooperation between regional boards and teaching hospitals in all regions, to ensure that there is a high standard of care available to the community, including a regional postgraduate training and research centre for emergencies and for accidents. At the hospital level such rationalisation will certainly involve the closing of many casualty departments as they are at present conceived, and will require special understanding from management committees and hospitals.

5. Nowadays a hospital (or indeed, the hospitals) serving an area can rarely exist in isolation in providing the kind of medical care which, to be effective, must be a continuous process. Because of the recent growth and development of industrial health services there is a need for future hospital arrangements to include provision for close cooperation with such services, strengthened, perhaps, by clinical assistantships in hospitals for industrial medical officers.

6. Equally, the service provided by general practitioners has a bearing on the way in which casualty departments are used by the public. Because of the importance of providing a service for the relatively minor, non-urgent conditions, there is need for the fullest consultation between the hospitals and local medical committees (and other appropriate bodies) as to how general practitioners can help to relieve the hospital of the burden of such cases, and so enable the hospitals to concentrate on what they are best fitted to do. The question of employing general practitioners as clinical assistants should be explored, not only because there is undoubtedly a shortage of suitable junior staff, but because such a move would strengthen the essential links between the hospital and community services.

7. It is difficult to generalise about the kind of organisation required by the hospital service to meet the needs of any one region, or even community, because there is insufficient information available at present about the variation in frequency and type of casualties in the case-loads of departments. Certain main principles are put forward . . . as fundamental to the arrangements for dealing with urgent accident and emergency cases. The most important is that there should be full twenty-four hour cover by doctors adequately trained for the work they are called upon to do, and who are assured of the stability and importance of this phase of their medical career. The organisation needed will obviously vary from area to area and facts should be obtained about the incidence, and in particular the kind, of emergencies and accidents coming to the hospital in each area.

8. It would be a mistake to assume that all the relevant facts can be easily gathered by simple statistical methods. To obtain the necessary background information, regional hospital boards should, in association with teaching hospitals, consider setting up multi-interest surveying teams, properly constituted and consisting not only of practising clinicians but others with experience in the interpretation of demographic data. Such teams should have secretarial help and be properly advised on statistical, sociological and administrative matters, as well as on organisation and methods. They should also have wide terms of reference, to include not only the study, in all areas of a region, of the organisation for dealing with major casualties —which in any case, because of the drama attached to them, may already be relatively well provided for—but also how the run-of-the-mill material which makes up the bulk of so-called "casualty work" is at present being dealt with. They should also look at this work in relation to the other services of the hospital, including rehabilitation and resettlement arrangements, and to the effect of prolonged and preventable disability on the individual and the community. In view of the increasing problem of cross-infection, special regard should be paid in such surveys to the control of sepsis.

9. Methods for helping the work of such surveying groups should be developed, including systems of records designed to produce relevant, up-to-date information. A method of noting features of casualty departments, capable of further development as necessary, is suggested for use by such groups; and an account is given of a simple records system—specially designed for sampling—to extract the basic data needed for the study of the range and depth of the work of casualty departments.

10. In view of the poor accommodation in the newer departments visited, it is strongly recommended that the functional requirements of casualty departments should be carefully studied in conjunction with all practising personnel, and the results applied in new buildings, as well as in the adaptation of existing accommodation.

3. Seale, J. R. *Lancet*, 1959, ii, 555.

# Points of View

## SPORTS MEDICINE

J. D. G. TROUP
M.R.C.S.

SPORTS medicine is not a recognised specialty in this country, yet the need for it is obvious. Medical centres, where research for sport is going forward, exist in Finland, Sweden, Russia, and West Berlin. In them investigations are made into the physiology, the psychology, and the statistics of sports medicine. It would be absurd to say that the United Kingdom lags behind in sport for lack of medical sport specialists, but it is certain that a very useful contribution towards training methods, and hence performance, could be made. But that is not all, because what can be learnt from sport has a tremendous bearing on some of the illnesses which come under the vague heading of rheumatism, and probably on others besides.

In this country medicine only provides a supervisory service for sport. It attempts to advise on the prevention of permanent damage, and to provide first-aid facilities and rehabilitation after injury. Medicine is not very clever when it comes to coping with the sprains and strains to which athletes are subject. If these lesions do not heal on their own, or after a period of rest, the athlete has to give up. There must be many hundreds of athletes and sportsmen who, because of a recurrence of symptoms whenever they begin intensive training after resting, have had to discontinue all but the gentlest activity. Very little is understood of these injuries, and their diagnostic labels are among the most meaningless in all medicine. This is partly because disappointingly little is known about the mechanics of the body, and therefore doctors are correspondingly inept at treating the disabilities which arise from mechanical strains. We know practically nothing of what renders a joint unstable, unbalanced, and hence subject to injury. Consequently we are in no better position to advise the sportsman how to avoid injury and strain than are his trainers.

* * *

This is important to Medicine because the minor injuries and strains to which the athlete is subject are closely related to some similar conditions which are classified as rheumatism, fibrositis, lumbago, "neuritis", and so on. These conditions take up more of the profession's time than practically any other single group of diseases, and they all have one thing in common—they represent deviations from the normal mechanical efficiency of the body. The symptoms of which the athlete complains can be easily cured if he gives up athletics; but the same thing in the tired middle-aged housewife has to be palliated and endured.

Thus the more we can learn from the disabilities and difficulties experienced by athletes, the more we are likely to help the tired middle-aged housewife to be less tired and to forget that she is middle-aged. One of the most unfortunate things a doctor can say to a patient is: "Well, you are not as young as you were, and you have to expect some aches and pains. After all your joints don't last for ever; it's just fair wear and tear." This reassuring information, coupled with advice to take it easy and to rest, is only practical if the patient had been entertaining fears of malignant disease. Otherwise it means that the doctor does not know how to help.

This may seem unfair to those who, in all good faith, have found no way of relieving a patient's symptoms, and who are confronted by palpable evidence of degenerative processes. Osteoarthritis has got to begin somehow. Though essentially a degenerative process it must be preceded by such factors as loss of function, local circulatory failure, or neurodystrophic processes, or by a combination of all three. If the history is taken carefully and exhaustively, almost invariably one finds that the process began with a minor injury, an attack of lumbago, or some other sprain type of lesion—the sort of lesion which can be the result of a minor injury or some repeated strain, and of which healing was incomplete. A man may sprain an ankle, though not badly enough to seek medical advice; and after the first flush of inflammation has subsided, he remains symptom-free provided he does not exert himself. Many people never do exert themselves, and such people commonly adopt unconsciously some postural deviation, which relieves the strain from the unhealed lesion but which imposes a mild chronic strain elsewhere. Furthermore, one-sided muscle weakness is bound to follow the loss of function and the adoption of a postural fault. Degenerative processes could well begin like this; and they do, loss of function being the key ætiological factor.

* * *

The average young man of sedentary habit, if otherwise healthy, can easily cover a mile in 10 minutes if pushed to it. After a week's training he can probably do it in 6 or 7 minutes; and in a month or so, if driven, in 5 or 6 minutes. But if he wants to run a mile in 4 minutes, he must train intensively for a long time; he would probably have had to begin in his 'teens, gradually improving his performance as he gained experience of competitive athletics.

In rather the same way a patient with a disability, such as an osteoarthritic hip, has to go into training if he wishes to overcome the disability and live a normal life. The onset of osteoarthritis in the hip commonly dates back to an injury causing low-back pain and pain and weakness in the leg—an injury which probably caused a sacroiliac lesion or strain. The patient clearly never recovered full function after the injury, and the stiffness of the hip and associated pain developed from that time. In practice, even when the osteoarthritis is advanced, it is worth trying to relieve the loss of function which set off the osteoarthritic processes. An arthritic can gain remarkable relief and improvement if he is prepared to "go into training". The trouble is that, once the disability is there, he has to keep in training.

A mass of information is already available on how to increase the strength, bulk, and endurance of muscles, and on related factors such as reaction-time and speed of contraction. But what we want to know is something about the strength of muscles or muscle groups which act on a joint, and their relation to injury of that joint, the suppleness of the joint, and all the interrelated factors affecting joints under stress. If "sports medicine" can answer these questions, we shall learn a great deal about treating sports injuries, about athletic training methods, physical education, the prevention of joint degeneration, and about the treatment of the common skeletal aches and pains.

In a report[1] in which the contribution of sports to medicine is discussed, the World Health Organisation refers rather vaguely to "functional disturbances of

1. World Health Organisation (1959) Preliminary Report on Sports Medicine (reprinted in the Physical Education Yearbook 1959–60).

autonomous regulation . . . (which) . . . form a considerable proportion of the clientele of practising physicians . . . (and for which) . . . evidence suggests that physical exercise, suitably in the form of sport, is a valuable means for the prevention and treatment of such disturbances". This is a beginning, though, as contributions to the subject go, not a very stimulating one.

* * *

The advance of civilisation is changing our way of life at a speed which is gathering momentum. The process began with the growth of domestic architecture and the installation of furniture, and has sped along with the help of the easy chair. It began with the introduction of the horse as a means of transport, and is accelerating as buses, motorcars, trains, mechanical handling, and automation take hold. But the evolution of Man has gone on over a length of time which makes the few centuries of civilisation seem but a moment, and it will take us tens of thousands of years to evolve into an animal which is adapted to this life of cushioned idleness. We cannot wait that long. The sooner we get down to it, and learn the extent to which our wellbeing depends on the mechanical and functional efficiency of the body, the better. "Sports medicine" is more likely than anything else to provide the answers.

## Public Health

# ACUTE COPPER POISONING

## An Outbreak Traced to Contaminated Water from a Corroded Geyser

A. B. SEMPLE
V.R.D., M.D. Glasg., D.P.H.
MEDICAL OFFICER OF HEALTH, CITY AND PORT OF LIVERPOOL

W. H. PARRY
M.D. Lpool, D.P.H.
PRINCIPAL MEDICAL OFFICER (EPIDEMIOLOGY), CITY OF LIVERPOOL

D. E. PHILLIPS
M.R.C.S.
ASSISTANT MEDICAL OFFICER, CITY OF LIVERPOOL

DURING the past eighteen years, the number of cases of food poisoning from all causes has risen from 119 in 1941 to 7300 in 1958. Although the majority of these were attributed to salmonellæ, many (21,501) causes remained unidentified, and only 27 during that period were attributed to chemicals.

We have recently investigated an outbreak of 18 cases of acute gastroenteritis traced to copper contamination of water from a canteen geyser. The mode of this contamination leads us to believe that this form of poisoning may be more common than is supposed.

### THE OUTBREAK

On June 10, 18 of 150 workers in a Liverpool factory collapsed with moderate to severe gastroenteritis after drinking tea in the factory canteen. Their symptoms, consisting of severe abdominal pain with vomiting and diarrhœa, headache, and dizziness, which occurred either immediately or within five to ten minutes of drinking tea, suggested an acute chemical poisoning.

2 of the victims were so collapsed that they were admitted to hospital for twenty-four to thirty-six hours. Chemical analysis of their fæces showed the presence of copper in concentrations of 80 and 50 parts per million (p.p.m.). A diagnosis of copper poisoning was made. Over the next four weeks, regular chemical analysis of their fæces showed decreasing quantities of copper, confirming the diagnosis of acute rather than chronic copper poisoning.

### SOURCE OF COPPER POISONING

The tea was prepared in large aluminium teapots, each holding sufficient tea for 18 cups; the water was boiled in a gas-heated geyser. All 18 victims had drunk tea from the same teapot; this being the last pot of tea made that morning. Unfortunately, the residue of the teapot had been discarded, but the geyser which supplied the water was tested. 3 pints of water were drawn off and macroscopically this sample showed a brownish tinge due to suspended particles of matter with a similarly-coloured sediment. Chemical analysis showed that this was due to suspended particles of copper sulphate. The water was very slightly acid (pH 6·7) and the total copper in suspension was 44 p.p.m.

The geyser was now dismantled and examined. It consisted of a gas-heated all-purpose water boiler holding 10 gallons. Externally it was chromium-plated, but the inside part of the boiler and lid was made of copper. Examination of the internal parts showed a blue-grey deposit of copper sulphate encrusted over the top of the boiler lid and around the opening for the float control arm. The boiler was cleaned and re-assembled. The result of chemical analysis of water from the geyser after cleaning was negative for copper.

### DISCUSSION

We can trace only three recent references to illness attributable to copper contamination of water from geysers:

Griffin [1] reported an outbreak in which drinking water had become contaminated from a corroded geyser. Copper in drinking water was responsible for an earlier outbreak where the water had been boiled in a large untinned and unlined copper.[2] More recently, in 1956, 5 cases of acute copper poisoning occurred in a factory canteen and this outbreak was apparently due to copper salts from a gas geyser, which had contaminated water stored in it overnight and used to make tea the following day. In this outbreak it was established that copper salts from the flue could have fallen into the water. The water used for the tea was not available for examination, but a further sample yielded 10 p.p.m. of copper.[3]

In this Liverpool outbreak, drinking water was again contaminated by copper salts from a corroded geyser, and it is interesting to examine the reason why only 18 persons were affected out of the 150 who were at risk.

For the purpose of tea making, there were six $4^1/_2$ pint aluminium teapots in use and tea was prepared by putting a $1^1/_2$ oz. packet of tea in each teapot and adding boiling water from the geyser as required. When the geyser was dismantled for examination, a heavy deposit of copper sulphate was found on the upper and inner cover of the copper boiler. To one side of this cover there was a circular hole (2 in. in diameter) to give access to the arm of the float. Close to this hole there was a bare patch from which it was concluded that a portion of the copper sulphate had recently broken off. This chemical deposit may have been dislodged from the lid by some sudden disturbance such as the jarring of the teapot against the boiler outlet-tap, so causing the copper sulphate to fall through the hole into the boiling water, and, the tap being

1. Griffin, A. J. B. *J. R. sanit. Inst.* 1951, **71**, 1.
2. Hebblethwaite, A. S. *Publ. Hlth*, 1928, **41**, 276.
3. *Mon. Bull. Minist. Hlth Lab. Serv.* 1957, **16**, 241.

open, the current of flow may have enabled the chemical to pass from the boiler through the tap into the teapot. If this is the correct explanation of the presence of copper in the teapot, it would account for there being only 18 victims out of 150 who were served with canteen tea on that particular morning.

The geyser in this canteen was of a type that is in common use. The makers state in their maintenance manual that in hard-water districts the interior surface of the boiler would require cleaning every three to four months to remove the scale deposited. In soft-water districts, they state, there is rarely any necessity for internal cleaning; servicing, when required, is reduced to the cleaning of burner and flue-ways, renewal of all valve washers, regreasing of gas cocks, and to adjusting the automatic gas-valve. No mention is made specifically of the formation of copper-sulphate deposits. Inquiry showed that this particular geyser had never been dismantled for cleaning or scaling, and it had been in constant use since 1949.

SUMMARY AND CONCLUSIONS

An outbreak of 18 cases of gastroenteritis occurred in a Liverpool factory canteen owing to the contamination of tea by copper from a corroded geyser.

We recommend that this type of geyser should carry a revised maintenance instruction booklet, indicating the possibility of the formation of copper-sulphate deposits and the methods by which these deposits can safely be removed. This form of maintenance should be carried out every three to six months.

We wish to thank Mr. J. F. Clark, Analyst for the City of Liverpool, for the chemical analysis of the tea water and the fæcal specimens.

### Food Hygiene

New Food Hygiene (General) Regulations,[1] made jointly by the Minister of Health and the Minister of Agriculture, Fisheries, and Food, consolidate the Food Hygiene Regulations 1955–57, with some small amendments, which include: (1) the application of the regulations to the handling and service of food on board certain ships and vessels; and (2) the relaxation of some of the requirements relating to temperature at which certain foods must be kept in catering premises. The regulations come into force on Oct. 1.

In the new Food Hygiene (Docks, Carriers, &c.) Regulations [2] the most important differences from the Food Hygiene (General) Regulations include the following: (1) a distinction is made between the obligations of persons allocating accommodation for handling food and those of employers who occupy the accommodation for handling food; (2) the obligations of dockers and porters as to cleanliness, clothing, &c., are limited to occasions when they are handling food which is not packed in such a way as to prevent the food from coming into contact with any surface that the package may touch; (3) certain requirements relating to structure and washing and sanitary facilities are less stringent; and (4) the primary obligations with regard to structural requirements at premises have been placed on the owner. The regulations come into force on Nov. 1, except for some which may involve alterations to premises or equipment. These are deferred until May 1, 1961.

### Certification of Stillbirths

In England and Wales from Oct. 1, doctors and midwives certifying stillbirths will be required to state the cause of death.[3] This is already required in Scotland.

1. S.I. 1960, no. 1601.
2. S.I. 1960, no. 1602.
3. S.I. 1960, nos. 1603, 1604.

## Conferences

### NUTRITION

THE fact that President EISENHOWER took the trouble to attend the opening session of the Fifth International Congress on Nutrition, held in Washington from Sept. 1 to 7—and made a cogent speech in which he pointed out that transferring food from one country to another as a gift might seem to the recipient to be a good and altruistic act, yet at the same time it could ruin the economy of a third equally deserving country—underlines the importance to the world today of food and the science of nutrition.

The congress also showed that large international meetings can be organised without their purpose being swamped in the sheer traffic of the numbers attending. At Washington there were between two thousand and three thousand people from sixty-odd countries. The meetings were primarily arranged as a series of panel discussions of previously printed communications; but all this led up to a full day's plenary session to consider the world's food needs and the food resources available to meet them. This was opened by the U.S. SECRETARY OF AGRICULTURE, who came, as Mr. Eisenhower had come six days before, to emphasise again how much depended on the wise application and development of scientific knowledge.

Prof. JAMES BONNER (California Institute of Technology) said that, if the present rate of growth continues unchecked, the world's present population of 2900 million will be doubled in the year 2000; and, if we do not check it by conscious design, the present rate of breeding must stop at any rate by A.D. 2660, because by then the entire land area of the globe will be covered by people standing shoulder to shoulder. When the epidemic of science and technology strikes a nearly stable population, the death-rate plummets and numbers shoot up until the birth-rate falls too. In Japan, the lag between these events was 90 years. If this time-scale is applied to the whole world today, an almost stable population of 15,000 million can be expected in 90 years. If the world's population could be checked at under 10,000 million, it could be fed.

#### Protein

The new maturity in nutrition—the welding together of the analytical and the humane—was well exemplified in the panel discussing protein. Dr. N. S. SCRIMSHAW and Dr. R. BRESSANI, of the Institute of Nutrition of Central America and Panama (INCAP) in Guatemala City, described work on protein undernutrition—so-called kwashiorkor—in children. It was idle for the Victorian physician to recommend a poverty-stricken mother to take her ailing child to Egypt for the winter; it is equally unrealistic today to advise poor Central American children to drink a pint of milk a day. Instead, the INCAP workers, after considering the specific aminoacid deficiencies of the diet on the one hand and the available supplies of local protein foods on the other, have devised a mixture of ground maize, sorghum, cottonseed flour, and dried yeast, suitably enriched with vitamin A and calcium, which is being successfully marketed in Guatemala and elsewhere and eagerly eaten as the sort of gruel to which people are accustomed. The therapeutic effect on malnourished children with kwashiorkor is as good as that produced by milk.

In the panel specifically discussing maternal and infant feeding, Dr. PAUL GYÖRGY compared the nutritional value for infants of human milk on the one hand and cow's milk and a number of other substitutes on the other, and Prof.

R. F. A. DEAN (Uganda) discussed further aspects of the problem of protein malnutrition.

Prof. D. B. JELLIFFE and Dr. F. J. BENNETT (Uganda) emphasised once more that the science of nutrition, when it is applied to the practical problems of human life, human behaviour, and human disease, cannot be treated as a science apart if it is to be effective. Besides understanding biochemistry and physiology, the public-health nutritionist must know about the culture patterns of the people with whom he is dealing and must operate within the framework of their ideas, attitudes, and beliefs. The nutritionist faced with a case of kwashiorkor knows that the sick child, by being sent to stay with relatives, is being deprived of protein; but he is a better public-health worker if he is also aware that by leaving home the child may be gaining his inheritance, and a good education as well.

### Processing and Additives

Food technology exerts a very direct effect on nutrition, whether the diet is made up of the sort of foods to which we are accustomed in wealthy and sophisticated cities or whether it comprises cottonseed flour for village children in Central America. It was understandable, therefore, to find a panel discussing the effects of processing and additives on food.

This discussion was opened by Dr. S. K. KON (Reading), who talked about cow's milk and deplored the atmosphere of sanctity which had hung about it and frustrated even such simple and desirable technological acts as pasteurisation. Now that it can be more clearly seen that people in the rich section of the world may actively harm themselves with creamy milk, while those of the poor majority in other parts must protect themselves against the hazards of infection, there is force in Kon's prophecy that the future for liquid milk is to be dried.

Nowadays, the impossible task of proving the negative proposition that something added to food is harmless is taken as proved when it is shown that animals suffer no harm when fed, not twice, or sixteen times, or even sixty times, but the tidy factor of one hundred times the amount of the material in question that people could reasonably expect to eat. This axiom is now hallowed by the approval of an F.A.O./W.H.O. Expert Committee. Clearly, food technologists must take precautions to ensure that the foods they produce are safe; but, as Dr. B. L. OSER (New York) pointed out, a balance must be maintained, and harmless, nutritious, but uneaten food contributes less to nutrition than the same article presented more colourfully and less decayed and consequently eaten.

### Domestic Animals

The nutrition of domestic animals has a double interest: study of their own physiological needs advances the science of nutrition, and their husbandry contributes to the supplies of human food. At the Washington meeting both these aspects were reviewed.

Prof. E. J. BIGWOOD considered the often paradoxical situation in which in some parts of the world the population of farm animals, which should support the inhabitants of the area, may in fact be in competition with the human population. If animals are raised as part of the food-supply, it is obviously important that they be raised efficiently.

Mr. E. J. UNDERWOOD (Western Australia) considered the implications of the fact that over large areas of the Earth's surface nutritional disabilities affecting the productivity of grazing stock are now known to occur. Doctors have sometimes found themselves envying their veterinary colleagues, despite the fact that animals cannot recount their own symptoms. It is, therefore, worth noting Underwood's conclusion that in animals, as in man, naturally occurring nutritional deficiencies seldom exist in simple or uncomplicated form.

### Ischæmic Heart-disease

While most of the panel discussions were concerned with various aspects of the clamant needs of the underfed majority of the world's population—a majority which only strenuous efforts will prevent from increasing as the population doubles in the remaining 40 years of the century—one was set aside for discussing the most striking nutritional problem of the surfeited minority, among whom we British are numbered. This is the sharply rising death-rate of men from middle-age onwards from ischæmic heart-disease.

The case was fairly put by Dr. E. BRONTE-STEWART (Cape Town). If it is accepted that ischæmic heart-disease results from atherosclerosis—and this has yet to be proved—there is evidence from epidemiological studies to suggest that a disordered lipid metabolism is in the background, and that this disorder can be accounted for by a dietary fatty-acid imbalance. Although alterations in the serum-lipids can be induced by changes in the dietary fat intake, it has yet to be shown whether or not such alterations have any bearing on the disease. Nevertheless, the dietary fat hypothesis remains a good working hypothesis, because, of all the environmental variables that constitute our present-day mode of life, no other at present known can be so closely related to the pathological, metabolic, and epidemiological features of the disease.

### Germ-free Animals

While the panel discussions were dealing with the urgent practical problems of today's crowded Earth, never less than five simultaneous sessions were in progress at which an immense variety of 10-minute research papers were read. As remarkable as any were some of those presented during the two full sessions devoted to studies of germ-free animals.

The devising of the technique by which an operator, dressed in a sterilised rubber diving-suit, delivers a lamb by cæsarean section, and, after sterilising the animal, posts it through an air-lock into the sterile compartment in which it is to live, must command the respect of other investigators. At the University of Notre Dame, a germ-free lamb was successfully reared for 60 days but gradually failed during the next 60—demonstrating that there is much in nutritional science still to be discovered.

MAGNUS PYKE.

## ORTHOPÆDICS

THE eighth congress of the Société Internationale de Chirurgie Orthopédique et de Traumatologie was held in New York on Sept. 4–9, under the presidency of Prof. J. TRUETA (Oxford).

### Congenital Dysplasia of the Hip

Prof. BRYAN MCFARLAND (Liverpool) said that in assessing treatment it was necessary to have certain criteria as to the degree of dysplasia, the age of the patient, and the grade of result. He had laid down three types—the mildest dysplasia, moderate displacement, and frank dislocation. He defined five grades of results—I, perfect; II, good; III, some mild persisting dysplasia; IV, subluxation; V, complete redislocation. He believed that dysplasia was not confined to the bones but extended to the soft tissues, and it was this which often caused poor results and late arthrosis. Treatment should be as early as possible. Manipulative reduction must be gentle without anæsthetic; and, if this was impossible, open reduction was carried out.

Dr. IVAR ALVIK (Norway) reported his findings in 945 typical dysplasia hips treated under the age of 7 years. 67% were bilateral. 736 hips were reduced by closed manual reduction, which was easily performed but had a high frequency of redislocation and osteochondritis. Interposition of soft tissue was due to capsule or limbus, but he had never seen the limbus inverted in a hip previously untreated. Open reduction was done in 206 hips, but in only 71 as a primary procedure. He now advocated gradual reduction by traction, and open reduction only when this failed. Immobilisation in the "frog position" had now been abandoned and a more moderate position with some internal rotation was used. Early weight-bearing was responsible for osteochondritis and deficiency of the acetabular roof; weight-bearing should be delayed for two years, sometimes longer, until the os acetabuli

was well developed. Excessive anteversion, if present, should be corrected by osteotomy.

Dr. OSCAR SCAGLIETTI (Italy) discussed the place of open reduction of the dislocated hip. Closed reduction was unwise in children aged 4–5 years, or if the degree of dislocation was severe; if closed reduction failed, open reduction was necessary. The exposure should be ample and should be on the Smith-Petersen approach. Muscles which were tight should be discarded and the psoas tendon, which was the commonest cause of obstruction, should be lengthened. Good results were obtained in 68% after five years' follow-up. The best results were obtained between the ages of 1 and 3 years and if the hip had not been previously treated.

Prof. MARINO ORTOLAND (Italy) discussed early diagnosis and the pathological changes to be found in the fœtus and at the time of birth. His findings were based on postmortem dissection of 50 pelves of fœtuses or newborn children, some premature. He said that dysplasia was always bilateral, though on one side it might regress and subsequently be unrecognised. Frank unilateral dislocation might occur during intrauterine life and was no greater in those with associated deformities than in those without them. The dual formation was due to a primary constitutional hereditary factor and a secondary environmental factor which was essentially mechanical. This might act during intrauterine life or shortly after birth. Diagnosis by clinical methods was to be preferred to radiology, which was unreliable. The most reliable clinical signs were a positive "click test" and the finding of limited abduction. As a result of laxity of the capsule the limbus was progressively flattened and a secondary acetabulum might be formed.

Dr. PAUL C. COLONNA (U.S.A.) said that in young children abduction treatment, started early, was often successful; but as the child began weight-bearing the results became progressively worse. The debatable age for treatment was 3–8 years, when changes in the acetabulum and capsule were established. If the acetabulum was severely flattened and shallow, he advocated a capsular arthroplasty. First, relaxation of contracted tissue was obtained by manipulation, subcutaneous tenotomy of the abductors, and skeletal traction until the femoral head was opposite the acetabulum. At operation, the acetabulum was deepened by being scooped out, and the capsule of the joint, which had been carefully preserved, was stitched over the femoral head and the head reduced into the enlarged socket. If anteversion was excessive, this was corrected by a supracondylar osteotomy five weeks later. A plaster cylinder from groin to ankle was applied so that active hip movements could be started. Careful postoperative care to restore function was essential.

Dr. KNUD JANSEN and Dr. E. H. J. LORSEN (Denmark) said that they had used arthrography routinely to assess the effect of treatment. 2 ml. of contrast medium was injected under anæsthesia. If the limbus was seen to be inverted this might indicate incomplete reduction and a poor final result, but Severin had shown that even in these circumstances a good result could be obtained. Repeated arthrograms would show the adaptation of the limbus. There was some evidence that osteochondritis might follow injection of contrast medium. In such cases the ligamentum teres might have been damaged accidentally.

Dr. G. HAUBERG (Germany) described the results of 330 early acetabular-roof arthroplasties in which a wedge of bone was introduced just above the acetabulum. He showed that the effect of this wedge was not purely mechanical but that it actually stimulated growth of the roof.

Dr. W. MOHING (Germany) said that a valgus position of the femoral neck resulted in deterioration of the hip-joint. There was always a tendency for valgus to increase, and if this was beyond 130° a varus osteotomy would be done. It might be necessary to repeat it later if recurrence took place. Rotation osteotomy would often be accompanied by varus.

Mr. F. C. DWYER (Liverpool) said that osteochondritis of the femoral head was a not uncommon complication of the treatment of congenital dislocation of the hip. If weight-bearing allowed the deformity, aggravated and severe flattening of the head was noted. He advocated the use of a patten-ended calliper for two years, and longer if necessary.

Mr. E. W. SOMERVILLE (Oxford) emphasised the importance of finding the basic primary factor which led to dislocation of the hip and dissociating from it the secondary deformities which developed later. An arthrogram would show that in a subluxation the acetabular roof was not sloping or defective, and it could be shown that the deformity of the acetabulum in dislocation was secondary as was the anteversion of the femoral neck. Laxity of the capsule resulting from prenatal parental hormonal influences was the likely cause of the instability. In these circumstances there was a strong case for not allowing extension of the hips of all infants, under any circumstances, from the moment of birth for some weeks.

Prof. ISHIHARA MIKI (Japan) said that the early diagnosis of congenital dislocation of the hip was very difficult. He did not believe that the click sign or any other sign was infallible. He described cases in which apparently normal hips subsequently became dislocated and where abnormal hips underwent spontaneous healing. The only way of being certain regarding stability of the hips was to take X-rays with the hips in such a position that any instability would be exaggerated.

Dr. SOPHUS VON ROSEN (Sweden) said that examination of children at birth between 1952 and 1960 had disclosed 39 cases of congenital dislocation of the hip. Treatment was by splintage in abduction continuously for two to three months. Laxity of the joint capsule was the probable cause of dislocation; and his colleague Dr. Lars Andren had found that in children with dislocated hips there was an associated laxity of the pelvic ligaments generally which could be demonstrated radiologically. This might be associated with the relaxing parental hormones which developed before birth.

Dr. ROBERT D. SALTER (Canada) considered that in all cases of unstable congenital dislocation or sublaxation of the hip the acetabulum was defective because it was, as a whole, facing the wrong way. He described an operation in which, after open reduction of the head into the acetabulum, the pelvis was osteotomised immediately above the acetabulum by means of a Gigli saw passed through the sciatic notch. The gap was widened anteriorly, and a bone graft taken from the region of the anterior superior spine was wedged in it to keep it open. The position was stabilised by the introduction of a Kirschner wire and the hip immobilised in plaster for six weeks. The longest follow-up was two and a half years, and to date the results had been very good. It was interesting that the anteversion angle did not need correction after the hip had been stabilised.

Dr. PAUL A. PEMBERTON (U.S.A.) described an operation for rapid and certain correction of the instability of a dislocated hip. He carried out a partial osteotomy of the pelvis above the acetabulum, levering the lower fragment down over the femoral head and keeping it in position by wedging in a bone graft. He had found that the operation gave better results in a short period of time and with fewer complications than other methods.

Dr. WILLIAM S. SMITH (U.S.A.) described observations on dogs in which dislocation of the hips was produced. Typical dysplasia followed these artificial dislocations whether the dislocation resulted from open operation or closed stretching of the capsule. If, after dislocation, some foreign object was put into the acetabulum in place of the femoral head, dysplasia did not develop. These findings suggested that dysplasia resulted from the absence of the femoral head from the acetabulum and was not therefore primary.

Dr. BECKETT HOWARTH (U.S.A.) said that subluxation and dislocation of the hip was prevented by a strong intact capsule. Elongation of the capsule, perhaps of hormonal origin, was the primary factor leading to displacement. First, the head was displaced laterally and later upwards. The capsule might be stretched in vitro. The displacement might increase after birth. Other changes found in the acetabulum and femur were secondary.

## Osteogenesis in Relation to Delayed Union and Pseudarthrosis

Dr. HAROLD B. BOYD (U.S.A.) said that bone was a specialised form of connective tissue, which accounted for its ability to join by formation of new bone. Whereas other tissues all joined by fibrous tissue, the mechanism of bony union was at molecular level and was not yet understood. He reported 1013 bone grafts in 842 patients with 94% ultimate success, though in 64 patients the operation had to be repeated. As would be expected, pseudarthrosis was uncommon in the young; but when it occurred it should be regarded much as a congenital pseudarthrosis. In the results the highest rate of success was obtained by means of intramedullary nail and bone graft and the lowest by a plate and bone graft, but there was not as much difference between the methods as might be expected. The cause of failure in the tibia and forearm was usually infection, and in the humerus and femur fracture of the graft. For union to occur, osteogenesis was essential. This was promoted by contact, fixation, and compression. It was further greatly helped by cancellous bone packed around the fracture. Both experimentally and therapeutically, autogenous grafts were better than homogenous and should always be used unless there was some contraindication.

Dr. R. JUDET (France) said that bone healed like any other connective tissue. Healing occurred in four stages: (1) initial resting stage, (2) proliferative hypervascular stage, (3) recessive hypovascular stage, and (4) stage of consolidation and cicatrisation. Non-union occurred if any of these stages did not develop. If the vascular hyperplasia failed an avascular type of non-union developed, whereas if this stage persisted too long the connective tissue failed to mature and a hypervascular pseudarthrosis developed. As the vascular reaction subsided the mineral-salt content of the connective tissue increased. Environment played a big part in this sequence of events, which could easily be hindered by vascular damage, infection, or the introduction of foreign materials.

Dr. J. JUDET (France) described a method of treating pseudarthrosis by compression, which he said released from the connective tissue between the bone-ends certain substances which promoted union. It was necessary therefore that this connective tissue should in no way be damaged. No plaster fixation was necessary and sepsis was not a contraindication. If necessary, the compression could be combined with a graft. Union occurred in uncomplicated cases in four months and in septic cases in six months.

Prof. ROBERT D. RAY (U.S.A.) said that individual reaction to trauma varied greatly, but generally speaking, provided the trauma was within reasonable limits, cell proliferation was stimulated. This reaction to trauma had been used clinically in many ways. Intermittent compression acted as a stimulus, but the effect of continuous compression was still unknown. Evidence supported the view that when bone was transplanted a certain number of cells survived, though this depended on the type of graft used. High-speed dehydration reduced this variability. Dead-bone transplants afforded immobilisation, acted as a barrier to scar tissue, and formed a matrix on which new bone could form. There was some evidence that this last function was facilitated by decalcification of the graft.

Discussing non-union of long bones, Prof. MERLE d'AUBIGNÉ (France) reported his findings in 820 patients. In 94% union was ultimately obtained, though not always by the first operation. The use of a bone graft combined with intramedullary nail fixation was the best method in the humerus and femur because no plaster cast was required. It was less good in the forearm and tibia. The essentials for union were good bone contact and long-continued and complete immobilisation.

Dr. J. D. RAMADIER (France) described an operation in which pseudarthrosis of the tibia could be repaired even if some sepsis was still present. This consisted in a tibiofibular synostosis performed at the fracture site, the graft being applied to the front of the fibula and the back of the tibia. 30 such operations had been done.

Two contributions described methods of storing bone for long periods. Both agreed that deep-freezing was the best method but that some other method was often more practical. Professor GUNTZ (Germany) described the use of 'Cialit' solution in the preservation of bone grafts. The grafts were removed aseptically and all soft tissue was removed. They were placed in the solution and were ready for use three weeks later. To date they had remained sterile for three years. Experimentally these grafts were a little slow to incorporate for two to three weeks but in the end were as fast as any other homogenous bone. They had been used in 800 operations.

Professor IDELBERG (Germany) described another method of bone preservation. In this the grafts were placed in special cases and immersed in 'Polacos' preserver of the consistence of a paste. This set hard with the graft in the centre of the block, which could easily be stored at room temperature. The grafts when used were almost as good as deep-freeze bone.

Mr. R. G. TAYLOR (Oxford) reported 72 bone-grafting operations in 68 patients with malposition and non-union of fractures of long bones. These were taken from a total of 16,700 fractures treated between 1950 and 1955 at Oxford. The commonest bone was the tibia; secondly, the radius; and thirdly, the femur. He advocated the use of the sliding graft whenever possible. If a further portion of graft was available, it should be laid alongside the fracture, and any gaps were filled with cancellous bone. If alignment was satisfactory, the fibrous union was not disturbed. Bony union was obtained in 97%. The failures were both due to sepsis.

Professor TRUETA said that in general he supported the views of Judet and Judet, but had himself found little evidence to support the idea of "hypervascular" non-union. Vascular penetration of the bone from the surrounding periosteum was the deciding factor, and the vascular wall took a most active part in producing new bone beyond the preliminary state of calcified cartilage. The nutrient artery was always ruptured in a fracture and became thrombosed. The periosteum was raised from the bone so that the ends of the bone died. Cartilage cells developed on the ends of the bone and were invaded by blood-vessels. That union should take place depended on the ability of these vessels to invade the cartilage and dead bone.

Professor OTOLENGI (Argentine) said that the Phemister graft was well recognised as a means of bone grafting. Chutro had in fact described this type of grafting many years ago, and he felt it should be renamed the "Chutro-Phemister" graft. The principles were: (1) an autogenous cortical graft was taken with a chisel and (2) placed across the fracture subperiosteally; (3) fibrous union was not disturbed; (4) there was no metallic fixation, and (5) immobilisation must continue until consolidation.

Dr. G. W. N. EGGERS (U.S.A.) said that the healing of fractures was obtained by complete metaplasia of the anaplastic fibroblast. This was affected by certain physiological factors and was undoubtedly stimulated by compression. He described an experiment which clearly demonstrated this. The best force of compression was that resulting from voluntary-muscle tone which should be utilised whichever method of immobilisation was employed. Care must be taken that any form of internal fixation did not interfere with this factor of compression.

Dr. EDWARD L. COMPERE (U.S.A.) said that substances taken by mouth or injected locally into the fracture would not help bony union. The most important factor in obtaining bony union was the preservation of the blood-clot. Open operation should never be done unless there was some strong indication for this. Rigid immobilisation was not necessary for union, and any rigid internal fixation which prevented continuous compression might cause delay. If compression was too powerful it would cause bone absorption and delayed union, and the ideal degree was that provided by the tonic contracture of muscles. Early weight-bearing was a further stimulus. If a fracture had to be opened it was logical to try to promote union by removing chip and sliver grafts from the adjacent bone and laying them across the fracture.

# In England Now

*A Running Commentary by Peripatetic Correspondents*

OLD Doctor Tom must have had a way with him. Like getting blood out of a stone it was to run a private practice in his day. Or so he used to say. All very well to get paid with a pound of butter or a couple of dozen eggs, and maybe a pig at Christmas: perhaps no income-tax on the perks, but hard at first to replenish his little stock of drugs, let alone pay off the mortgage on the house. He solved that one by engaging a housekeeper who had a sister in the next village with a thriving general store. So pills turned into butter, and butter into shillings, and shillings to pills once more in the best Economics tradition. I do not suppose that he would ever have paid off the mortgage on such slender margins of profit if his only other rival in the valley had not come to an untimely end at the crossroads by the Post Office. The acceleration of a pony and trap had failed miserably to compete with one of those new horseless carriages. Doctor Tom put on a black tie and took over the gentry from the vacant practice. The guineas must have rolled in after that. The house was his, all spick and span, with a new double garage later on where the stables used to be. Bessie no longer slipped out of the back door with the butter and eggs: they were needed for the servants downstairs. And when the time came they laid him out on the waiting-room couch, in his best frock coat and his silk cravat. The countryfolk filed past to stack their wreaths around the walls. Doctor Tom must have known it was market day. Peeping between the chrysanthemums and the dahlias were some unmistakable pieces of farm-cured ham, a couple of dozen eggs, and an outsize slab cake. No wonder he looked so serene: he was going out where he came in.

• • •

Our New York taxi-driver described, to our great interest, his forthcoming lunch, which would consist of ham and eggs. "But," he exclaimed with great emphasis, "I only eat three eggs a week as eggs contain cholesterol and cholesterol causes atherosclerosis." "Is this general in the United States?" we asked. "Oh, yes," he replied, "particularly if there has been any history of heart disorder in the family. I don't eat any animal fats and have only margarine, not butter, but three eggs a week are quite safe as the newspapers have told us so."

Perhaps that is why eggs are only half a crown a dozen in the United States.

• • •

As I have encroached already on the money I hope to get when our rise comes through, it seemed time to economise—but on what? Smoking, clothes, or entertainment? No, being rather overweight the obvious thing was food. I suppose I must have mentioned casually to my friends about living on eggs and baked beans and spaghetti on account of my perilous financial state.

Last week a porter sidled up to me: "I've left a parcel in your office, doctor." Trying not to show my excitement, I went upstairs. There was an enormous newspaper parcel; inside, a lettuce. I was thrilled—a free supper. That night I ate the whole lettuce and a hard-boiled egg; it was satisfying, but dull, as there was nothing to go with the lettuce. The following day, the occupational therapist knocked on the door. "I'm going on holiday, and heard you liked lettuce. It seems a shame to waste these." In her outstretched hands was an even bigger newspaper parcel—two lettuces nestling inside. On my way home I stopped at a shop and bought a small bottle of mayonnaise. For two nights I had lettuce and mayonnaise. By the fourth day I was longing for spaghetti again, but lettuces continued to arrive. The word had gone round the whole hospital by now: "The doctor loves lettuce."

In the last few days I have bought ham, pilchards, salmon, cucumber, tomatoes, radishes, salad oil, vinegar, garlic, and mustard. I have also had to stop smoking, buying clothes, and going to the pictures.

• • •

I support with enthusiasm the humanitarian suggestion to establish a regular column on diseases recently discovered not to exist. But a few questions come to mind. How should priorities be assigned for the discovery that a well-known disease does not exist? The mere claim that one has never seen it should not suffice, but it is admittedly hard to *prove* that one hasn't seen it. Who discovered first, for instance, that the Fröhlich syndrome does not exist? What kind of proof is acceptable for showing that a disease one has often read about *never* existed? How shall we deal with people who say "But I definitely remember a case I saw seventeen years ago . . ."? Should young doctors be encouraged to discover diseases that do not exist? Can we encourage iconoclasm in an ancient and revered profession? Again, what shall we do about "diseases" that are common but confuse the doctor since they rarely make his patient ill, such as œsophageal hiatus hernia?

Meanwhile here are my suggestions for this week's list of diseases that should pass into history: Bürger's disease; Van Neck's disease (ischiopubic osteochondritis); and calcaneal apophysitis in growing children with painful heels.

• • •

The Island steamer was making its daily placid way from the mainland to the various island ports of call, and informal calls they were, and are, and (I hope) always will be.

The group on the pier usually included the "post", the piermaster of course, often the police constable, and sometimes the nurse or doctor to collect polio vaccine. There is always the usual freight to be left—mails, bread from the city, newspapers, and miscellaneous household and farm goods of all kinds. Some places have no pier—yet—and the ferryboat came out to meet us, rising and falling in the Atlantic swell: when it left our side it was noticeably lower in the clear green water with its cargo of passengers, mailbags, and so on, and maybe a calf in a bag with its head showing. I have seen a car too on the ferryboat and very cranky it looked.

At one of the smaller piers the duties of the piermaster, postman, brake-driver, rope-thrower, and handyman were combined in one person who was appropriately dressed in dungarees and wellingtons, a postman's jacket, and a taxi-driver's cap. When we were ready to depart the Skipper leaned over the wing of the bridge and called down to him "Right, Dougie, let go". Down below on the pier, the foreshortened figure of the factotum—holding a struggling sheep between his legs—looked up and said plaintively "Ye're in an awful hurry the day, Hughie: can ye no gie us a minute tae look round?" "You're just a damned nuisance Dougie," said the Skipper agreeably and began to fill his pipe while Dougie in rapid Gaelic exchanged news with the deckhands at the stern, and Her Majesty's mails waited till everyone had savoured the local gossip. Then, and only then, did Dougie condescend to cast off.

• • •

The first day's proceedings of the symposium were bearable because the organisers had thoughtfully arranged for a copy of *What's On In London* to be placed on each delegate's chair. By the second morning, however, this literature had been enjoyed to the full and there was nothing for it but to listen to the communications or browse through the abstracts. I felt obliged to sit through each session, if only to forestall the gibes of my adhesive colleague who delights in remarking on a late arrival or early exit. But on the last day, mercifully, the symposium split into double sessions, held in separate halls, and I was able to slip away unmolested to attend Dr. Picasso's demonstration.

• • •

My peripatetic pardner had best get his facts strate afore he openz his noo Saloon. Wes Hardin was not at the O.K. Corral, and Doc Holliday never dug no bullets out of him.

• • •

*From a patient's card:*

Sept. 9—catheter in situ.
Sept. 10—catheter out of situ.

Rather like Mr. Lumumba somehow, don't you think?

# Letters to the Editor

## ATHEROSCLEROSIS AND CORONARY HEART-DISEASE

SIR,—Dr. Gordon (Sept. 10) very reasonably expresses horror at the idea of feeding humans 1500 calories a day in the form of butter, and questions whether the animal experiments described by Dr. Gresham and Dr. Howard (Sept. 3) warrant their implication that in man coronary thrombosis and coronary atherosclerosis are independent in their ætiology.

I have recently completed an epidemiological investigation of coronary heart-disease in a population sample of over 220 men aged 65–85 years, and have come to the same conclusion as Dr. Gresham and Dr. Howard. Very briefly my reason for this is that when these old men with symptomatic and electrocardiographic evidence of coronary heart-disease are compared with their coevals who do not have this complaint, they lack several of the characteristics which have been found [1–3] in younger men with coronary heart-disease. They do not have higher serum-lipids, they do not smoke more cigarettes, nor have they expended less physical effort at work. Recent research indicates that the most important factor in the pathogenesis of coronary heart-disease in young men is increased coagulability of the blood,[4] and that this is associated with a high serum-lipid level [5 6]; high serum-lipids in turn occur in heavy cigarette smokers [7 8] but are reduced by physical exertion.[9 10] Taken with epidemiological studies [11–14] this work suggests that most of the rise in mortality in coronary heart-disease is due to an increase in the incidence of acute coronary thrombosis, the often lethal condition of middle-aged men, but that coronary atherosclerosis without a major thrombus can cause chronic signs and symptoms later in life; that the former has been shown to be associated with disturbed lipid metabolism but the latter has not. There is nothing new in this; nearly ten years ago Morris [11] theorised that a separate ætiology for coronary thrombosis and atheroma could be the only reasonable explanation for his finding that the amount of coronary atherosclerosis in the population has changed little over the past century, although mortality from coronary thrombosis has risen.

It is impossible to express this argument logically yet succinctly (I hope a full report will be published early next year), but the important point is that laboratory investigation on the one hand and a field study on the other have led two independent groups of workers to the same conclusion for different—but I hope valid—reasons.

London School of Hygiene and Tropical Medicine, London, W.C.1. ROY M. ACHESON.

1. Gertler, M. M., White, P. D. Coronary Heart Disease in Adults. Cambridge, Mass., 1954.
2. Morris, J. N., Heady, J. A., Raffle, P., Roberts, C., Parks, J. *Lancet*, 1953, ii, 1053, 1111.
3. Doll, R., Bradford Hill, A. *Brit. med. J.* 1956, ii, 1071.
4. McDonald, L., Edgill, M. *Lancet*, 1957, ii, 457.
5. McDonald, G., Fullerton, H. *ibid.* 1958, ii, 598.
6. Maclagan, N., Billimoria, J., Curtis, C. *ibid.* p. 865.
7. Dawber, T., Kannel, W., Revotskie, N., Stokes, W., Kagan, A., Gordon, T. *Amer. J. publ. Hlth*, 1959, 49, 1349.
8. Karvonen, M., Kemp, A., Orina, E., Fidanza, F., Brozek, J. *Lancet*, 1959, i, 492.
9. McDonald, G., Fullerton, H. *ibid.* 1958, ii, 600.
10. Cohen, H., Goldberg, C. *Brit. med. J.* 1960, ii, 509.
11. Morris, J. N. *Lancet*, 1951, i, 1.
12. Thomas, H., Cochrane, A., Higgins, I. *ibid.* 1958, ii, 540.
13. Brown, R., Davidson, L., McKeown, T., Whitfield, A. *ibid.* 1957, ii, 1073.
14. Brown, R., McKeown, T., Whitfield, A. *Brit. med. J.* 1958, i, 555.

## VIRAL ÆTIOLOGY OF MOUSE LEUKÆMIA

SIR,—I read with interest your recent survey [1] of virus tumours of mice [1] and I trust you will allow me to make the following comments:

In the initial experiments dealing with inoculation of filtrates prepared from leukæmic mouse tissues into newborn mice of the C3H strain, it was observed in 1953 that some of the inoculated mice developed leukæmia, while others developed neoplasms of the parotid glands.[2] It was relatively easy, however, to separate that same year the respective causative agents by differential heating, ultracentrifugation, or use of filters of different porosity; the leukæmic agent was larger, heavier, and less resistant to heat than the parotid-tumour virus.[2 3] Furthermore, it was later found that the parotid-tumour virus, but not the leukæmic agent, is resistant to ethyl ether.[4]

The fact that the parotid-tumour virus is widely prevalent in normal healthy mice was also established early in these studies.[5] Many oncogenic viruses are carried by apparently healthy hosts; such viruses may remain latent through the lifespan of their carriers. Some, however, become activated and cause neoplasms. Such activation may occur spontaneously, or may be prompted by various factors, such as ionising radiation, or certain carcinogenic chemicals. A potentially leukæmogenic virus is also widely prevalent in many normal mice. Thus, mice of the C3H or C57 Brown strains remain in most instances, if undisturbed, free from spontaneous leukæmia. Fractionated total-body X-irradiation will, however, induce leukæmia in some 50 to 60% of such mice. From donors with radiation-induced leukæmia the leukæmic virus could be recovered, and passed by inoculation to newborn mice, transmitting the disease.[6]

Spontaneous activation of the leukæmic virus in mice occurs now and then, and is particularly common in certain inbred strains of mice. The parotid-tumour virus, on the other hand, remains as a rule latent when carried by naturally infected and undisturbed hosts. Spontaneous development of parotid tumours in mice is exceedingly rare. Yet the development of such tumours in natural carriers, such as non-inoculated C3H mice, could be prompted by treatment with cortisone [7] or by total-body X-irradiation.[8]

The recovery of infective and transmissible leukæmic viruses from natural mouse carriers is not always an easy matter. Many such carriers, when used as donors, yield filtrates of low infectivity, or no infectivity at all. It was therefore of considerable practical importance that a virus strain could be developed from spontaneous Ak leukæmia which now induces a practically 100% incidence of leukæmia following inoculation into suckling mice of a susceptible strain such as C3H or C57 Brown/cd.[9] Similar leukæmic mouse virus strains were also developed from transplantable mouse tumours.[10 11]

I cannot agree with those [12] who question the viral nature of the leukæmia-inducing factor present in such filtrates. The leukæmogenic factor is a particle, which can be readily sedimented in an ultracentrifuge.[13] This particle is thermolabile, and can be easily destroyed by heating to 56°C or even only 50°C for 30 minutes.[14] The particle is pathogenic, and induces a specific disease in susceptible hosts; its infectivity spectrum is limited to certain species and even inbred lines of hosts. Some of the leukæmic virus-strains recovered from, and carried routinely in, mice can, however, also cross species barriers and cause lymphosarcomas following inoculation into newborn rats.[15 16] After inoculation into susceptible hosts (i.e., new-

1. *Lancet*, July 23, 1960, p. 200.
2. Gross, L. *Proc. Soc. exp. Biol., N.Y.* 1953, **83**, 414.
3. Gross, L. *Cancer*, 1953, **6**, 948.
4. Gross, L. *Acta hæmat.* 1956, **15**, 273.
5. Gross, L. *Proc. Soc. exp. Biol., N.Y.* 1955, **88**, 362.
6. Gross, L. *ibid.* 1959, **100**, 102.
7. Woolley, G. *Proc. Amer. Ass. Cancer Res.* 1954, **1**, 53.
8. Gross, L. *Acta hæmatol.* 1958, **19**, 353.
9. Gross, L. *Proc. Soc. exp. Biol., N.Y.* 1957, **94**, 767.
10. Graffi, A., Bielka, H., Fey, F. *Acta hæmat.* 1956, **15**, 145.
11. Moloney, J. B. *J. Nat. Cancer Inst.* 1960, **24**, 933.
12. Miller, J. F. A. P. *Brit. J. Cancer*, 1960, **14**, 83.
13. Gross, L. *Ann. N.Y. Acad. Sci.* 1957, **68**, 501.
14. Gross, L. *Acta hæmat.* 1960, **23**, 259.
15. Graffi, A., Gimmy, J. *Naturwissenschaften*, 1957, **44**, 518.
16. Moloney, J. B. Personal communication, 1960.

born or suckling mice of strains C3H or C57 Brown/cd) the leukæmic virus strain developed in our laboratory [9] induces leukæmia in practically all injected hosts; it can then be readily recovered from such hosts and passed indefinitely by serial inoculations. In normal C3H or C57 Brown/cd mice it consistently induces lymphatic leukæmia. If thymus is removed from inoculated hosts, the resulting leukæmia may appear later and be of the myelogenous form,[17] not previously observed in mice of this strain. Filtrates prepared, in turn, from donors with myelogenous leukæmia and inoculated into newborn C3H mice induced again the usual form of lymphatic leukæmia.[14]

The leukæmogenic factor present in such filtrates is a thermolabile, self-reproducing, pathogenic agent, which can be seen as a spherical particle less than 100 mμ in diameter in the electron microscope,[18] and which, in all probability, belongs to the broad group of oncogenic viruses.

Cancer Research Unit,
Veterans Administration Hospital,
Bronx, New York. LUDWIK GROSS.

## TUBERCULOSIS: A SOCIAL STIGMA

SIR,—Mr. Foster-Moore's letter (Sept. 10) attracts my sympathy, as I had similar feelings (for similar reasons) many years ago.

I can well remember, after a period of successful treatment, failing to secure an appointment because a medical officer on the staff I wished to join insisted (though he had never met me and sought no particulars) that he was not prepared to accept the risk of working with an "ex-T.B.". Fortunately, subsequent colleagues have been more enlightened, and I can assure your correspondent that the picture, now, is not as gloomy as he paints it. Though some prejudice certainly exists—and while patients who behave in the way he describes are with us some wariness is understandable—it is certainly not generally true that ex-patients, if their disease is well healed, "will never be able to obtain a position which involves a medical check-up", nor that "if a job is superannuated, they have little chance of acceptance". As the medical officer of health responsible to my county authority for advising on acceptance or not of candidates for employment I can say that local authorities in general (I cannot speak for all) are concerned only with two points: (*a*) will the candidate be able to give reasonably continuous service in the post for which he has applied?; (*b*) is he likely to be a risk to those with whom he is to work?

Naturally, one must apply stricter standards under (*b*) to nurses, teachers, child workers, and so on, as is shown by the requirements of the Ministry of Education in respect of teachers; but to my personal knowledge there are now working in my county several teachers, nurses, child-care workers, and others who were accepted for service, under the superannuation scheme, after successful treatment for tuberculosis. Incidentally, not one of these, past or present, has broken down in service since.

An important point not mentioned by Mr. Foster-Moore is life assurance. Some companies refuse applications outright; others add a substantial loading to premiums, which becomes increasingly unreasonable as the years pass without any relapse. One large company, however, who took me on many years ago, use the excellent method of a decreasing lien—i.e., premiums are the same but the sum payable after death is substantially less than normal at first and gradually rises to the normal during a stated period. For example, there may be a 20% lien running off in 20 years; after this period the full benefit is payable. This method is specially suitable for those who have been tuberculous since it recognises the decreasing risk of relapse after the early years.

One more point for your correspondent: he should start with the firm intention that he will not attempt to hide, when making applications for posts, that he has had tuberculosis. If his disease is well healed he will certainly be able to find an intelligent employer, and in any case it is not possible in practice to deceive many people.

You will understand I do not wish to name my local authority, and I therefore ask permission to sign myself

C.M.O.H.

## PARTIAL PARATHYROID INSUFFICIENCY

SIR,—In their interesting article of Sept. 3, Dr. Smith and his colleagues state that after thyroidectomy in which some of the parathyroids were removed there may exist a condition of latent partial parathyroid insufficiency, which could be made complete by calcium deprivation. In my studies on the physiology of the parathyroids, from 1923,[1] in which the function of the parathyroids as regulator of the serum-calcium was established (and which seems to be forgotten by subsequent workers), partial parathyroidectomy in dogs (removal of 3 glands) produced a certain degree of partial insufficiency.

The serum-calcium was lowered to a minimum of 7·1 mg. per 100 ml. without tetany, but was restored to normal in a few weeks on a diet which included half a litre of milk. When the calcium-rich milk (0·6 g. Ca) was removed from the diet, the serum-calcium fell in most instances, independent of whether the diet consisted of meat or bread, margarine, and fat, but not below the critical level producing tetany.

It is interesting to compare this partial parathyroid insufficiency with the state of latent tetany produced by total parathyroidectomy in my dogs. After a critical postoperative period with continuous calcium administration, the dogs passed into a state of latent tetany with adaptation to a low serum-calcium (about 6 mg.) and behaved normally provided the diet contained half a litre of milk. Whenever milk was removed from the diet, serious tetany ensued simultaneous with a further lowering of the serum-calcium. Milk from which the calcium was removed had no protective effect. When the calcium content of the milk was restored, tetany disappeared and the serum-calcium increased to the former (low) value.

It was shown that life was possible without any parathyroids provided the diet contained a certain amount of calcium.

Exactly the same observations were made in patients accidentally deprived of all (?) their parathyroids by parathyroidectomy.[2] They adapted themselves to a low calcium level, and women even went through pregnancies and bore normal children when their serum-calcium was down to 6–7 mg. But shortage of calcium in the diet always produced tetany.

Medisinsk Avdeling B,
Rikshospitalet,
Oslo. H. A. SALVESEN.

## BROILERS

SIR,—Your annotation of Aug. 27 says that "[human] infections due to eating chicken meat seem almost unknown in Great Britain". An outbreak of salmonellosis due to food from a broiler shop has been investigated in this area and may be worth a brief description.

On May 19 an elderly man with diarrhœa in an infectious-diseases hospital was found to be infected with *Salmonella thompson*. This excited no comment because sporadic "thompsons" had been isolated fairly recently from two obviously unconnected persons. But on May 21 a family of 4 persons and another 2 individuals were shown to be infected with *Salm. thompson*; and on May 24 two families totalling 6 persons were all found to be similarly infected. All had had foods from a certain broiler shop in the town where they all lived. The manager of the shop and his assistant were examined and found to have *Salm. thompson* in their fæces; and some cooked chicken sampled at the same time also yielded the organism; but other food from the shop—stuffing, roast pork, and shell egg—were all free. The establishment, with the manager and assistant segregated, was closed.

17. Gross, L. *Proc. Soc. exp. Biol., N.Y.* 1960, **103**, 509.
18. Bernhard, W., Gross, L. *C.R. Acad. Sci., Paris*, 1959, **248**, 160.

1. *Acta med. scand.* 1923, suppl. VI.
2. *ibid.* 1930, **74**, 13.

In all, 35 persons were infected in this outbreak, the last case being found on June 6. 7 persons had only a single positive swab; 25 persons averaged $3^1/_3$ weeks' infectivity; and 3 are still positive more than 3 months since original infection. This outbreak was due to type 4; one of the two earlier sporadic thompsons had been type 10. *Salm. thompson* is said to have been isolated from living broilers at a packing station that supplied this barbecue.

The findings do suggest that in this affair the chickens rather than the manager were carrying the *Salm. thompson*. But how the organism escaped the consequences of cooking is a question. Perhaps this infra-red cookery is less effective and penetrating than is claimed for it.

Royal Infirmary, Blackburn. M. S. SPINK.

## FAILURE OF CORTISONE TO CORRECT IMPAIRED WATER DIURESIS

SIR,—The letter from Dr. Marks and Dr. Hornabrook (Aug. 27) on failure of cortisone to correct impaired water diuresis in patients with suprasellar tumours is interesting but might be even more so if further clinical and laboratory data were available.

What was the clinical status of the patients, were tests of anterior pituitary function performed, and what were the plasma-cortisol levels? The fact that exogenous steroids failed to restore the diuretic response to normal suggests that adrenal cortical and anterior pituitary function were normal. The authors conclude by suggesting "that in some cases of suprasellar tumour there is a failure to inhibit antidiuretic-hormone secretion in response to hæmodilution". Do they mean that the tumours have damaged osmoreceptors of the hypothalamico-hypophyseal system (the presence of which was postulated by Verney [1]) but affected only the detection of hypo-osmolarity of the blood? The occurrence of such a condition would be at variance with the long-held view that injury to any part of the hypothalamicohypophyseal system results in diabetes insipidus.[2] If the response to hyper-osmolarity of the blood is normal in their cases, then this would be the first clinical evidence to suggest that there are different osmoreceptors subserving the detection of hypo- and hyper-osmolarity.

This is highly speculative but information from Dr. Marks and Dr. Hornabrook on the response of their patients to simple dehydration, to intravenous hypertonic saline or glucose, and to nicotine may throw further light on this problem.

Their reference to H. J. Crow (footnote 2) should probably read: "*Brit. med. J.* 1955, ii, 401".

The New York Hospital, New York 21, N.Y. CRAIG D. BURRELL.

Bellevue Hospital, New York 16, N.Y. MARY E. GRANGER.

*** This letter has been shown to Dr. Marks, whose reply follows.—ED. L.

SIR,—I was interested to read the comments by Dr. Burrell and Dr. Granger on the observation that cortisone frequently fails to correct completely the impaired water diuresis in patients with suprasellar tumours which Dr. Hornabrook and I described. Although our findings are at variance with the long-held view that injury to any part of the hypothalamicohypophyseal system results in diabetes insipidus they are in agreement with the observations of others that impaired water diuresis may occur with suprasellar lesions with or without normal plasma-cortisol levels and urinary steroids.[3] In a personal communication Dr. D. Marrack informs me that he has confirmed and extended our observations.

The frequency of the abnormality described and the rarity of diabetes insipidus is demonstrated by the fact that urine production was abnormally low after a 1500 ml. water load in five of eight consecutive adult patients with craniopharyngiomas examined preoperatively. Diuresis was normal in three. In one of these three there was evidence of secondary adrenocortical hypofunction—mean resting urinary 17-hydroxycorticosteroid (17-O.H.C.S.) excretion was 3 mg. per 24 hours with a normal rise after corticotrophin—and myxœdema due to thyroid disease: goitre with a normal thyroidal $^{131}I$ uptake which was not increased by thyroid-stimulating hormone. After replacement therapy with cortisone and triiodothyronine there was a polyuria of 3–4 litres per 24 hours. Mild to moderate diabetes insipidus can be masked by coexisting adrenocortical hypofunction.[4 5] In these cases the water diuresis is normal despite clinical and chemical evidence of reduced glucocorticoid secretion: overt diabetes insipidus appearing when cortisone therapy is instituted. Despite the ability to produce a urine of specific gravity greater than 1·020 and a normal nicotine test, it is likely that in the case quoted above there was some impairment of antidiuretic-hormone (A.D.H.) secretion also.

WATER DIURESIS UNDER VARIOUS CONDITIONS IN A MAN OF 26 YEARS WITH A SUPRASELLAR TUMOUR (CRANIOPHARYNGIOMA) CONFIRMED AT CRANIOTOMY

| 1500 ml. water: route of administration | Date | Therapy | Total 4 hr. urine vol. (ml.) | % of dose | Comment |
|---|---|---|---|---|---|
| Oral.. .. | Dec. 22, 1959 | Nil | 158 | 10·5 (75–120) | $^{131}I$ uptake normal<br>17 K.S. 10·2 mg./24 hr. (8–22)<br>17-O.H.C.S. 4·9 mg./24 hr. (6–21)<br>Hb 13·3 g./100 ml. |
| Oral.. .. | Jan. 15, 1960 | Nil | 90 | 6·0 | .. |
| | Jan. 22 | Cortisone 25 mg. b.d. | | | Course of deep X-ray therapy begun |
| | | ,, ,, | | | |
| | | ,, ,, | | | |
| | | ,, ,, | | | |
| | April 24 | Cortisone 25 mg. t.d.s. | | | Vision deteriorating |
| Oral.. .. | May 9 | ,, ,, | 350 | 23 | .. |
| 1500 ml. 5% dextrose intravenously in 65 min. | May 11 | ,, ,, | 605 | 40 | Moderate diuresis at 18 hr. |

Figures in parentheses are normal values for sex and age.

The nine patients already reported were investigated on their admission to hospital for the diagnosis and treatment of intracranial disease. In the main their general health was good. None had renal, hepatic, or cardiac disease. Pituitary function tests were carried out and included the measurement of urinary neutral 17-ketosteroids (17-K.S.) and total 17-hydroxycorticosteroids [6] and $^{131}I$ studies. Plasma-cortisol levels were not measured.

Pituitary function varied from moderate hypopituitarism in three to complete absence of abnormality in two. The fact that cortisone when given in doses not normally causing polyuria but which are adequate for restoring water diuresis to normal in hypopituitarism produced some, albeit incomplete, improvement is further evidence that steroid deficiency was sometimes a contributory factor.

A man of 49 with moderate hypopituitarism caused by a craniopharyngioma (17-K.S. 3 mg., 17-O.H.C.S. 3·5 mg., $^{131}I$ uptake 43%) excreted 17% of the water load before treatment. A transient polyuria in which 2 litres of urine was excreted occurred within 12 hours of the first dose when steroid therapy was instituted a few days later. This was accompanied by a feeling of increased well-being. The water-diuresis test

1. Verney, E. B. *Lancet*, 1946, ii, 739, 781; *Proc. roy. Soc.* B. 1947, **135**, 25.
2. Fisher, D., Ingram, W. R., Ranson, S. W. Diabetes Insipidus and Neurohormonal Control of Water Balance. Ann Arbor, Mich., 1938.
3. Hokfelt, B., Luft, R. *Acta endocr., Kbh.* 1959, **32**, 177.
4. Wise, B. L. *J. Neurosurg.* 1956, **13**, 107.
5. Unpublished observations.
6. Nabarro, J. D. N., Moxham, A., Walker, G. *Brit. med. J.* 1957, ii, 1018.

remained abnormal, however, when it was repeated while he was still on cortisone therapy and also after its replacement by prednisone.

In another patient (cited by kind permission of Dr. D. Marrack) with a craniopharyngioma there was a residual inability to respond to hæmodilution with a diuresis after months of cortisone replacement therapy (see accompanying table).

Generally in these patients fluid intake is voluntarily restricted and the urine is hypertonic. The effect of deliberate fluid deprivation has not therefore been studied. Nor has the effect of an intravenous hypertonic saline, or nicotine, infusion [7 8] been studied regularly since brisk diuresis, upon the suppression of which the test depends, is seldom obtained.

Moderate diuresis often occurs during the night, some 12–18 hours after the ingestion of water. For this reason we believe that the hypothalamic secretion of A.D.H. is still, to some extent, homœostatically controlled by the osmolarity of the blood.

It is suggested that normally the neurosecretory cells in the hypothalamus elaborate and secrete A.D.H.[9] and that they cease to do so when stimulated by impulses transmitted from the osmoreceptors in response to hæmodilution (hyposmolarity). The similarity between this proposed system of A.D.H. regulation and the negative feed-back regulation of the pituitary trophins, whereby their production is suppressed by elevated plasma levels of the appropriate target-organ hormone, is apparent. Consequently it is unnecessary to postulate the separate existence of osmoreceptors for the detection of hyperosmolarity and hyposmolarity as suggested by Dr. Burrell and Dr. Granger.

The osmoreceptors and the neurosecretory cells are believed to be anatomically distinct, the connection between them being nervous.[10] Lesions of the hypothalamus which interrupt the neural pathways would thus cause a delayed, and impaired, suppression of A.D.H. secretion in response to hæmodilution (i.e., a release phenomenon). More extensive lesions, or small ones which damage the neurosecretory cells directly, cause diabetes insipidus. Such lesions commonly occur after surgery, and are commoner in children with craniopharyngiomas than in adults.[5]

The results do not exclude the possibility of an irritative lesion causing hypersecretion of A.D.H. by direct stimulation of the neurosecretory cells in the supraoptic and paraventricular nuclei.[11]

Department of Chemical Pathology,
King's College Hospital,
London, S.E.5. VINCENT MARKS.

## DOUBTFUL PROGRESS IN PSYCHIATRY

SIR,—How discouraging to read Dr. Cleobury's views (Aug. 20) when he says that the open-door policy "has, in fact, been made possible only through the agency of modern physical methods of treatment." In fact open-door policies in mental hospitals antedate the modern physical methods of treatment by at least 60 years, as has already been pointed out in your columns.[12]

The report of the Commissioners in Lunacy for Scotland for 1881 gives a very clear account of the successful institution of the open-door system.[13] Adolf Meyer pointed out in 1894 that "Morningside in Scotland and other asylums show clearly that not a single door in any ward needs a lock . . .".[14] The Peoria State Hospital in Illinois was completely open in 1906.[15]

Of course opening doors by itself does not constitute treatment, it merely removes one of the irritating factors preventing recovery and provides a milieu in which a programme of rehabilitation and resocialisation can be effectively carried out.

It has been repeatedly asked what caused the doors to be closed again. I suggest that this was in part due to the very adoption by mental hospitals of the "time-honoured methods of clinical observation and study in conjunction with laboratory technique and research" so highly commended by Dr. Cleobury, which tended to focus attention on the disease rather than on the patient, whose needs were apt to be forgotten.

Leicester is only 40 miles from Nottingham. Is there an iron curtain in between?

Lincoln, Nebraska. FRANK WINSTON.

## ACQUISITION OF STAPHYLOCOCCI BY NEWBORNS

SIR,—The interesting article by Dr. Wolinsky and others last week gives further point to my contention that nurses should wear gloves, of thin rubber and sterile, to overcome the ineffectiveness of ordinary hand-washing. The authors do not state how to overcome this danger of spread "predominantly from the hands of the carrier to the infant." My letter [1] shows how to do it and why.

Pathology Department,
St. Margaret's Hospital,
Epping. FRANK MARSH.

## MORTALITY DUE TO BLOOD-TRANSFUSION

SIR,—I should like to compliment Mr. Graham-Stewart on his interesting article of Aug. 20, and to comment on his statistic regarding death-rates due to transfusions. He stated: "the mortality has been estimated as one to every 1000-3000 transfusions (Guynn and Reynolds 1958). This estimate was based on figures from leading (hospital) centres, and in hospitals as a whole the mortality may be higher." A review of the literature indicates that this figure is based on studies dating from 1917 to 1941, as the following synopsis will show:

This particular statistic of one death from every 1000 to 3000 transfusions has been frequently quoted. Checking article references, I found that in the February, 1958, issue of *Surgical Clinics of North America*, Guynn and Reynolds (p. 19) and Gibbel (p. 45) both used this figure. Their reference was an article by C. V. Moore.[2] Moore's figures are based on statistics compiled by A. S. Wiener (*Blood Groups and Transfusions*, 1943) and Kilduff and De Bakey (*Blood Bank and the Technique and Therapeutics of Transfusions*, 1942). They based their mortality-rates of 1 death in every 1000–3000 transfusions on studies dating back to 1917.

I have therefore attempted to determine a current valid statistic regarding death-rates from blood-transfusions. Information from the Ministry of Health and Blood Transfusion Centres reveal that over 3,500,000 units of blood were issued to the various hospitals in England and Wales for the five years 1954–58. According to statistics in the Registrar General's *Statistical Review of England and Wales*, there were only 8 deaths due to blood-transfusions reported during this period. If we assume that as much as 20% of the blood issued was not used, there were 8 deaths in 2,800,000 transfusions—1 death in every 350,000 transfusions.

In my own country, the United States, the Bureau of Vital Statistics recorded 234 deaths due to blood-transfusions in 1957 and 1958. During these two years, approximately 6,000,000 transfusions were given. Therefore, there was 1 death in every 256,000 transfusions.

It is encouraging to note that deaths from blood-transfusions are relatively rare today. From the above data, it can be estimated that there is 1 death in every 250,000 to 350,000 transfusions. It is not my meaning,

7. Cates, J. E., Garrod, O. *Clin. Sci.* 1951, **10**, 145.
8. Lewis, A. A. G., Chalmers, T. M. *ibid.* p. 137.
9. Bargmann, W. *Endeavour*, 1960, **19**, 125.
10. Landgrebe, F. W., Ketterer, B., Waring, H. *in* The Hormones (edited by G. Pincus and K. V. Thimann); vol. III, p. 395. New York, 1955.
11. Andersson, B., McCann, S. M. *J. Physio.* 1955, **129**, 44P.
12. Gibson, J. *Lancet*, 1954, ii, 1017.
13. Tuke, D. H. *in* The History of the Insane in the British Isles; pp. 376–378. London, 1882.
14. Report to the Governor of Illinois. Springfield, Aug. 2, 1894.
15. Pollak, M., Baer, W. H. *J. Hist. med.* 1953, **8**, 56.

1. *Lancet*, 1958, ii, 588.
2. *J. Amer. med. Ass.* 1952, **149**, 1613.

however, to infer that I condone the indiscriminate use of blood-transfusions. These comments are offered as a clarification of the current mortality-rate from blood-transfusions and to erase the use of statistics which date from 1917.

London, S.W.5. J. HARRIS JOSEPH.

## DISPOSABLE UNDERPADS FOR INCONTINENT PATIENTS NURSED AT HOME

SIR,—The letter of July 23 by Dr. Roberts and Miss Mann interested us not merely because we too manufacture disposable incontinence pads, but also because it is possible to use them with greater saving in cost than your correspondents indicated.

The size of the pads mentioned, 30 × 23 in., is larger than may always be necessary, and for this reason we make pads of 24 × 16½ in. Purchased in bulk, they cost approximately 4½*d.* each. From this it will be evident that, in a great many cases, it is far more economical to use such pads than to launder soiled linen. Where larger pads are required, there is perhaps little actual saving in money but a considerable reduction in labour. With smaller pads, there is economy in both ways.

Wheat Bridge Mills, Chesterfield. N. P. MANN
Development Manager, Robinson & Sons, Ltd.

SIR,—Incontinence pads have been used in the geriatric unit at Stobhill General Hospital since 1955. I understand that since 1957 they have been available in Scotland to general practitioners on prescription form E.C.10.

The pads are available in two sizes—12 × 16 in. and 16 × 18 in.—and are made of cotton-wool, cellulose, and non-absorbent grey wool. The pad is covered in gauze in order to prevent it adhering to the patient's skin. The cost to the hospital is approximately 6*d.* for the smaller size and 8*d.* for the larger size. I have been very satisfied with the type used.

The makers are Smith & Nephew—Southalls Ltd., 5, Singer Street, London, E.C.2.

Geriatric Unit, Stobhill General Hospital, Glasgow, N.1. W. FERGUSON ANDERSON
Regional Adviser in Diseases of Old Age, Western Regional Hospital Board (Scotland).

## PERITONEAL SPLASH: A PHYSICAL SIGN

SIR,—It is sometimes difficult to differentiate between perforated peptic ulcer and perforated appendicitis. Examination by radiography before operation is invaluable, but in certain circumstances may impose delay, and even expense, on a patient in pain. The differentiation is important, because the correct placing of the incision makes surgical treatment of either condition easy.

To be able to demonstrate diminished liver dullness is useful, but there is a wide variation of the normal area of liver dullness. There is, however, an additional physical sign which can demonstrate the presence of air in the peritoneal cavity. The rigid abdomen of the patient relaxes under a general anæsthetic, and allows the contained free air and fluid to give forth a splash, if vibrated. The splash is not so localised as that of an intragastric succussion splash, and has a note more highly pitched, and more superficial.

As an example of the value of this physical sign, I would cite a recent case treated for Dr. J. A. Smart in the Victoria Hospital at Lewes, a general-practitioner hospital with good radiological facilities, but without resident staff. A young man was admitted suffering from severe abdominal pain, which had settled in the right lower abdomen. The history and physical signs were equivocal, but it was clear that operation was indicated. Anæsthesia was induced by Dr. H. Rice, and the abdomen was exposed on the operating-table. The sponge-holding forceps with the swab soaked in antiseptic was agitated gently but rapidly on the skin of the relaxed abdomen, a splash was elicited, and all doubts were solved. A perforated duodenal ulcer was patched through an upper midline incision, and the patient recovered quickly.

I have read no description of this sign, which helped in the management of this and other patients, and therefore ask you to publish this letter.

Hove. P. A. LANE ROBERTS.

## HYDROCORTISONE INHALATION IN ASTHMA

SIR,—Dr. Langlands and Dr. McNeill (Aug. 20) report that hydrocortisone by inhalation did not improve the lung function in their 10 asthmatic patients. They gave 15 mg. per day by 'Medihaler', and they were aware—although this is not mentioned in their paper—"that up to 50% of this amount may have been wasted" (personal communication). In my opinion, the medihaler technique may cause even greater wastage. Attention should therefore be drawn to the possibility that their negative result, which is in contrast to that of other authors,[1–3] may be due to insufficient dosage.

London, N.3. H. HERXHEIMER.

## SMOKING BY ADOLESCENTS

SIR,—Most doctors who have looked at the evidence must be convinced that children who start smoking are exposing themselves to a serious risk of lung cancer in later life. If they live in an industrial area in England, they also risk developing chronic bronchitis.

In our society we often prevent people from doing things they want to do, if it is agreed that the proposed action would be harmful to the doer; for example, we try to prevent people from committing suicide, becoming morphine addicts, or marrying under the age of 16. Nevertheless very few doctors have suggested that we should prevent adolescents from smoking if they want to, and most people will approve; freedom should not lightly be curtailed.

However, I for one find it difficult to understand why we allow freedom to the tobacco manufacturers to spend very large sums of money on advertising which is directly opposed to the truth as we know it. Much of this advertising is, moreover, directed by subtle psychological means to appeal to the fears and hopes of adolescents. As I see it, this kind of advertising is a systematic attempt to mislead the young for personal gain. It is really very difficult to know how to answer a fifteen-year-old boy who asks: "If smoking is as bad as you say, why don't the doctors tell the Government to stop cigarette advertising?"

Halstead, Essex. R. E. W. FISHER.

# Medicine and the Law

## Death after Wasp Sting

AT an inquest at Woodbridge, Suffolk, on a 68-year-old woman who died shortly after being stung by a wasp, it was stated that she had also been stung about a month earlier, when the only ill effect was swelling of a finger.[4] After receiving the sting which led to her death the woman complained of feeling faint and she started to tremble. A doctor was called, and within minutes adrenaline was administered; but the patient nevertheless died. A pathologist testified that the cause of death was anaphylactic shock, the patient having been sensitised by the earlier sting. A verdict of death by misadventure was recorded.

1. Brockbank, W., Pengelly, C. D. R. *Lancet*, 1958, i, 187.
2. Helm, W. H., Heyworth, F. *Brit. med. J.* 1958, ii, 768.
3. Herxheimer, H., McAllen, M. K., Williams, D. A. *ibid.* p. 762.
4. *East Anglian Daily Times*, Sept. 15, 1960.

# Obituary

## JOHN FOSTER GASKELL

M.A., M.D. Cantab., F.R.C.P., D.P.H.

Dr. John Gaskell, who died on Sept. 11 at Cambridge at the age of 82, had never engaged in private practice, but had chosen to remain for over twenty-five years an honorary physician and pathologist to Addenbrooke's Hospital.

The son of a distinguished Cambridge physiologist, W. H. Gaskell, F.R.S., he was educated at Marlborough, Caius College, Cambridge, and St. Bartholomew's Hospital. After qualifying in 1907 he held a house-appointment at Barts, and in 1911 he was awarded a Beit fellowship. For a time it seemed that he might follow his father in physiological research, for in 1913 and 1919 he published important papers on the suprarenals and on the sympathetic nervous system. But his acceptance of a demonstratorship in pathology at Leeds University gave a hint of what was to follow, and the rest of his publications were on pathology and experimental pathology.

In the 1914–18 war he built up in Salonika a much-needed bacteriological service; and his book, written jointly in 1916 with Michael Foster, the younger, on cerebrospinal fever is probably the best known and the most outstanding of his works. Cambridge contemporaries will also recall how, during a comparatively quiet spell in the war, he turned his R.A.M.C. unit into an amateur operatic company; and with the help of his brother officers, Dr. Ffrangcon Roberts, Dr. Charles Budd, and other Cambridge doctors, he staged a full-scale production of *The Mikado* which was so successful that it went on tour.

On his return to Cambridge in 1920 Gaskell was elected assistant physician and pathologist to Addenbrooke's Hospital. He was largely responsible for the early development of the pathological services there, taking an active part in the routine work, especially morbid anatomy and histology, until he retired in 1946. He published a series of papers on lobar pneumonia in which he carried the American work on experimental pneumonia a stage further by showing that it was the virulence of the pneumococci—which he could vary at will by mouse-passage—rather than the size of the infecting dose reaching the lung that decided the type of lesion produced. This work, which was the subject of his Bradshaw lecture to the Royal College of Physicians in 1927, threw much light, not only on the pathology of lobar pneumonia, but also on the localisation of the lesions in bronchopneumonia and terminal pneumonia.

C. H. W. writes:

"The double post of physician and pathologist, which was still practicable in those days, gave Gaskell insight into, and a wide knowledge of, the problems of disease—qualities which were invaluable to all those who worked with him or were taught by him. He was a physician of the old school who insisted on the importance of careful history-taking and thorough clinical examination. He had a dry humour and was curiously detached from the hurly-burly of modern life. He disliked innovations, and, being unmechanical, he endured rather than enjoyed the austere rides on his motor-cycle to and from work. He continued to live, so far as he was permitted, in the tranquil atmosphere of the Edwardian era. It suited his temperament, but no doubt it was partly the result of his inheriting the home of his childhood, a fine estate with beautiful terraced gardens on the chalk hills near Cambridge. This was the centre of his life and its purpose was to provide a home for his daughter and his three grandchildren on their frequent visits from abroad. He found fulfilment in his work on the soil until his strength failed only a few months before his death. We who are left feel that his passing marks the end of an epoch, characterised by weekends spent in cutting trees or playing tennis, in an atmosphere of serenity and spacious beauty.

"The sudden death in early childhood of his only son, and two years later of his wife, left a permanent mark, detectable perhaps in his somewhat reserved manner. But behind this lay a sensitive nature and a warm heart, and all who met him knew instinctively that this was a man of integrity and a trusty friend."

## ERNEST KENNETH MACDONALD

O.B.E., M.D. Lond., D.P.H.

Dr. E. K. Macdonald died on Sept. 13 in Leicester, where he was medical officer of health till his retirement earlier this year.

During the 1914–18 war he served as a surgeon sub-lieutenant and qualified from St. Bartholomew's Hospital in 1919. After a period in general practice he became an assistant medical officer of health in the public-health department of the London County Council, and in 1926 deputy M.O.H. for Barnsley. He was in turn M.O.H. for Keighley, Barnsley, and Stockport before he was appointed to Leicester in 1935.

Dr. Macdonald regarded the National Health Service Act as a challenge which offered chances of fruitful work to the public-health service. He particularly welcomed the opportunities it offered for health education, and a health education officer was early appointed in Leicester, and a continuous programme of health education developed. Dr. Macdonald produced an excellent colour film on the health services of the city. Most of the film he shot himself, and he spoke the commentary. Another useful method of disseminating information was the cartoon figure of "Dr. Fosse" (Leicester is on the Fosse Way), who was used to give advice on health subjects. Dr. Macdonald also recognised the possibilities of a good home help service. In Leicester all home helps were given a fortnight's training and good indoor and outdoor uniforms, and the social value of their work was stressed. Home helps were provided without charge for certain problem families.

Dr. Macdonald was for many years interested in deafness, and he invited the Ewings of Manchester to Leicester to see what might be done there to ascertain deafness early in young children. Sir Alexander and Lady Ewing were quickly convinced of the value of health visitors in this work, and a pioneer clinic for the ascertainment of young deaf children and their training was established in the city.

Dr. Macdonald's work in Leicester soon won him a reputation outside the city and he was asked to sit on many national committees. He had been, for example, a member of the Radium Commission, of the Ministry of Health Prevention of Blindness Committee, of the Ministry of Works Advisory Council on Building Research and Development, and of the committee controlling the Public Health Laboratory Service. His chairmanship of the Central Council for Health Education from 1948 to 1951 included the difficult transitional time when its finances were reorganised and local authorities came to play a larger part in its running.

A. I. R. writes:

"Dr. Macdonald had more than his share of bad health, but nothing daunted his spirit or affected his élan. A dynamic personality and leader, he was always full of energy, applying his very quick brain to problems which were brought before him, quickly familiarising himself with what might be new and finding a solution. He was a most cheering person to work with. A first-class administrator, he always seemed to be a step ahead of most people in his ideas and means of putting them into practice. Until illness restricted his activities he had led a most

active life—surf-riding, sailing, playing badminton, caravanning. He was also a competent photographer and a keen gardener."

Dr. Macdonald leaves a widow and three daughters, two of whom are doctors.

### ALBERT VICTOR JOHN RICHARDSON

K.B.E., C.B., B.A., M.B. Dubl., D.P.H.

Air Marshal Sir Victor Richardson, who was director-general of the Royal Air Force Medical Services from 1938 to 1941, died on Sept. 16 at the age of 76.

He was the son of Lieut.-Colonel T. F. Richardson of the 5th Royal Irish Fusiliers, and he was educated at Trinity College, Dublin. After graduating M.B. in 1908 he entered the Royal Navy. During the 1914–18 war he served with the R.N. Air Service and ultimately transferred to the Royal Air Force when it was formed. In 1919 he was already a wing-commander, and in the same year he was appointed O.B.E. After successive promotions he had reached the rank of air vice-marshal when he was appointed director-general of the R.A.F. Medical Services in 1938. He held this appointment in difficult years of expansion and anxiety, but under his guidance the service effectively coped with heavy responsibilities. He was promoted K.B.E. in 1939. After he retired he became chief casualty services officer at the headquarters of the London Civil Defence region, and he held this post till the end of the war.

Sir Victor Richardson was twice married. His first wife, by whom he had two daughters, died in 1929. His second wife, formerly Miss Eileen Hornibrook, survives him with a daughter.

### Sir GORDON GORDON-TAYLOR

F. G. B. writes from New Zealand:

"I first met Gordon-Taylor in 1916 during the Battle of the Somme, and thereafter till the end of the war our paths often crossed in the clearing-station zone and my regard and affection for him steadily grew. During the Passchendaele fighting of 1917 I was attached to a forward group of clearing stations at Brandhoek near Vlamertinghe and visiting surgical teams included Ernest Miles, C. H. Fagge, Rock Carling, and Gordon-Taylor. To live and work with older men of such high quality was a privilege and an education to juniors like myself; and of them all Gordon-Taylor stood pre-eminent, partly because of his surgical distinction and partly because of his innate kindliness, sympathetic understanding, and appreciative attitude towards the younger men: in short, he was like a respected and much admired elder brother, someone to emulate.

"Later on he came to New Zealand and Australia as anatomist to several visiting teams of examiners for the primary fellowship. Then in 1945 he visited us on a good will tour, which was more in the nature of a royal progress. I am sure the warmth of his welcome must have afforded an intense gratification to his modest and responsive heart. No British surgeon was better known to us and none could have provided a happier link between the old and the new. The key to his supremacy lay, as it did in those far distant war days, in his obviously genuine sympathy and understanding of the problems of younger men, and no one was quicker to give praise when due. His friendships ranged from contemporaries down the scale to examination candidates who became his friends overnight and sought his advice in their careers. I write this as a personal tribute to a dear and ever kind friend and I know that it expresses the feelings, in some part at least, of many others. If fate denied him the Woolsack, as he termed it, he had a more solid satisfaction in the affectionate regard of countless friends and admirers."

### Dr. MARJORY WARREN

M. L. I. writes:

"The news of Dr. Warren's death has come as a profound shock to all who are connected with geriatrics. Besides those who actually worked with her, many, like myself, who were trying to develop medical services for the aged, knew that we could always go to her with our problems and be sure of sympathetic and helpful advice, given freely with all the authority of her long experience. We came away encouraged by her support to return again when faced by another set of difficulties, certain to benefit once more from her warm interest and unbiased approach."

J. S., one of her colleagues at the West Middlesex Hospital, writes:

"Dr. Warren had spent virtually the whole of her professional career in the hospital service. When she came to the West Middlesex in 1926 her duties at first covered the whole of medical practice and it is believed that her inclination was then towards a surgical career. It soon became apparent to her that, though the elderly and chronic in her charge were well cared for and well nursed, much more could be done to help them to return to an active and useful life. Her interest in geriatrics was thus born at an early age, and she began to give more and more of her time to this pioneer work and made a number of valuable contributions to its literature.

"The war gave an impetus to this work, and, when peace came, as the specialty of geriatrics came increasingly to the front, she played an increasingly active part both in this country and abroad. But it was to her own hospital that her life's work and affection were chiefly given. To her department came visitors from all over the world and she trained a large number of doctors in her methods. Possessed of an attractive manner and strong personality, she was quite fearless in putting forward views which she considered right and did not hesitate to take a lead in righting wrongs however unpleasant the task might be. She seemed so full of life and energy and was quite tireless. Her death has been a heavy blow not only to her colleagues but to countless patients who have lost a devoted friend as well as a beloved doctor."

## Appointments

ANDERSON, A. M., M.B. Edin., D.P.H.: M.O., headquarters staff, South-Eastern Regional Hospital Board, Scotland.
GILLIE, ANNE K., M.B. Glasg., D.P.M.: assistant psychiatrist (S.H.M.O.), Clifton Hospital, York.
JUEL-JENSEN, B. E., B.M. Oxon., Cand. med. Copenhagen: M.O., United Oxford Hospitals.
LUBIN, M. M., M.B. Lond.: senior casualty officer, County Hospital, Lincoln.
MELLOR, M. R., M.B. Birm.: assistant M.O.H. and school M.O., Newcastle upon Tyne.
ROBERTSON, J. D., M.D. Edin., F.R.C.P.E., F.F.A. R.C.S., D.A.: consultant, department of anæsthetics, Royal Infirmary, Edinburgh.
SPAUL, G. F., M.B. Lond., D.P.M.: senior assistant psychiatrist, Coppice Hospital, Nottingham.

**East Anglian Regional Hospital Board:**

CHAUDHARY, G. A., M.B. Punjab: registrar in geriatrics, West Suffolk Hospital group.
HUNTSMAN, R. G., M.B. Cantab., M.R.C.P.: consultant pathologist, Peterborough, Wisbech, and King's Lynn hospital areas.
KAPUR, S. K., M.B. Nagpur, D.T.M. & H.: medical registrar, Papworth Hospital.
RAVERTY, S. J., L.R.C.P.I.: registrar in psychiatry, Suffolk mental hospitals.
TURNER, R. G., M.B. Glasg.: registrar in plastic surgery, regional burns and plastic surgery unit, West Norwich Hospital.

**Manchester Regional Hospital Board:**

DAVIDSON, I. W., M.B. St. And., F.F.A. R.C.S., D.A.: consultant anæsthetist, North Manchester, Booth Hall, and Monsall groups of hospitals.
DOWIE, ROBERT, M.B. Edin., M.R.C.O.G.: consultant obstetrician and gynæcologist, Barrow and Furness group of hospitals.
HALLACK, I. M., M.B. Cape Town, F.F.A. R.C.S., D.A.: consultant anæsthetist, Salford group of hospitals.
PECK, R. M., L.A.H. Dubl.: senior casualty officer, Royal Albert Edward Infirmary, Wigan.
ROSS, W. J., L.R.C.P.E.: senior casualty officer, Victoria Hospital, Blackpool.
SWITHINBANK, A. H., M.B. Lpool, F.R.C.S., D.A.: consultant general surgeon, Wigan and Leigh group of hospitals.

# Notes and News

## CHILDBIRTH HERE AND IN U.S.A.

"EXPLORING each other's point of view" may be described as the aim of the newly founded Anglo-American Society, whose first meeting took place in Cambridge on Sept. 7. The officers took care to explain that it was founded "not to duplicate existing societies, not for British doctors to invite American friends, but as a common enterprise by both; to promote social and professional liaison, and to examine attitudes, values and customs as they apply to medicine in both countries".

The aim was admirably met in the controversial subject, the Normal Pregnancy on Both Sides of the Atlantic, discussed under the chairmanship of Major JOHN HOLBROOK (Lakenheath).

Two main speakers presented the obstetric picture for Britain. Dr. C. R. F. MALLET (Ipswich) described the pre-eminent role of the G.P.-midwife liaison. "The midwives," he said, "are the backbone of obstetrics. Their skill and competence is very, very good; we rely on them throughout." But he said that "a cardinal point to bear in mind is that consultant advice is readily available at all times in the home or in the hospital, and that in emergencies there is always a bed in hospital". Dr. Mallet's summary covered all the features familiar to his British colleagues (though murmurs showed that not all of them agreed with his dismissal of routine weighing as of little value). In particular he made it clear that most doctors gave considerably more detailed supervision than is paid for by the National Health Service obstetric service rules. The role of the general-practitioner obstetric unit and especially of domiciliary delivery were of special interest to the Americans in the audience, as was the work of the flying-squad. They noted also the allowance to the mother of £17 10*s*. or £12 10*s*., for domiciliary or hospital deliveries respectively, and the current N.H.S. fee of £7 7*s*. to the doctor for his obstetric services.

Mrs. S. MEE, Cambridgeshire's county nursing officer, described the training and work of midwives. She pointed out that, on top of the full nursing training, these women had six months' specialised hospital and then six months' domiciliary work. "It is no part of their training to attend to abnormal midwifery, but they do see these abnormal cases and they learn to recognise them if they arise." As soon as an abnormality was found the doctor was notified. Mrs. Mee explained the close cooperation with the doctor, the restricted range of drugs that midwives could use personally, and the safeguarding machines which controlled the strength of nitrous oxide or trichlorethylene given. The work, she said, was very personal, covering antenatal and puerperal attentions as well as the delivery. Each midwife was deemed capable of coping with sixty mothers a year, and this figure was more or less maintained. England and Wales had some 16,500 midwives in actual practice, and great attempts were being made to increase this number.

Dr. DAVID PETERSEN (Lakenheath) gave the transatlantic view with verve and friendliness. Perhaps what most surprised his British colleagues was his statement that the United States had but five hundred midwives, and five schools for them. This small band were either training as supervisors or instructors or destined for work in mission fields or very remote areas.

On domiciliary delivery Dr. Petersen was polite but adamant. He deplored it. He taught the belief that if the obstetric emergency needed a hospital bed, then the patient should already have been in that bed. A number of emergencies always would occur in the twinkling of an eye. To sort out in advance those women needing hospital and those fit for home deliveries was not enough. Many a consultant might make an error in such evaluation, and all the more easily could the less specialised doctor.

American babies, then, were hospital-born; and this could happen in one of three ways. If the mother was indigent she could be treated as a charity case, through hospital clinics and wards. If she could pay she was looked after by family doctor in a hospital which allowed him this privilege. Or she could choose to be dealt with by the specialist obstetrician and so get not only his expert attention, but perhaps also a little status symbolism. Delivery by specialists was becoming more common, with patients less and less ready to accept the family doctor. "The kindly old doctor is passing from the scene just like the buffalo and the Indian."

When the patient was admitted in labour the nurse mainly checked the details of admission, and the patient was the doctor's. Episiotomies and low forceps were common. Once the baby had been born, and after twelve hours of rest, the new mother was extracted from her bed and considered to be fully ambulant. She remained three to five days only in hospital.

Dr. Petersen answered some pointed questions. He conceded and regretted that after she left hospital the mother had little close medical or nursing supervision. As to whether the patient's income affected the length of stay in hospital or the treatment given, he said: "We try not to let the financial influence our good judgment," but put a hesitant stress on the word "try". He was lukewarm on relaxation in labour, but "prepared to go along with such a plan if the patient was in quest of such discomfort". On the other hand, obstetric analgesia was very highly developed, with, he thought, far greater variation than in Britain since all obstetrics had hospital facilities.

Finally, he remained unconvinced about the role of the midwife. "I do not believe," he said quizzically, "that the best obstetrics can be practised with the doctor at home in bed." Yet in spite of the contrasting methods on each side of the Atlantic the figures for maternal and fœtal mortality and morbidity showed no significant differences.

In the discussion that followed, Captain MARTIN ROSNER showed himself moved by the British maternity allowances and also by the N.H.S. obstetric fees. "I find it rather paradoxical," he said in mock bewilderment, "that the patient gets paid more than the doctor does."

## CHARTERED SOCIETY OF PHYSIOTHERAPY

DURING the annual congress of this society, opened in London on Sept. 15 by Sir Robert Platt, P.R.C.P., a dinner was held on Sept. 16.

Dr. T. F. Fox, proposing the Society and its Founders, said that the latter would be happy to see how large the society is, to attend the congress illustrating the remarkable scope of its work, and to know that the professional status physiotherapists have long enjoyed is now to have statutory recognition. Miss Sybil Evans, responding as vice-chairman of council, pointed out that people with severe handicaps are no longer confined to bed or a cripple's chair, and physiotherapists were continuing their study of the part physiotherapy can play in preventive medicine, especially in the study of posture and lifting. State registration had been their object for forty years, but the profession had insisted on its right to self-government, with a majority of physiotherapists on the registration board. Though "the medical profession as a whole has not seen eye to eye with us here", physiotherapists were grateful for the continuing practical interest of doctors not only in the counsels of the society but in physiotherapy departments and schools.

Sir Cecil Wakeley, the president, welcomed The Guests, and Sir Arthur Porritt, P.R.C.S., replied. Pleading for more attention to the medicine of sport, he gave some account of the medical side of the recent Olympic Games, and spoke warmly of the determination of physiotherapists to work as members of the medical team.

Miss Evans paid a special tribute to the work of Sir Harold Boldero as chairman of council during six difficult years. The society was indebted to him for the great patience with which he had presided over a body of individualists, and for the help he had so willingly given wherever it was needed. "We have a great affection for you; and I can say that now."

The Founders' lecture was given on Saturday by Lord Taylor, F.R.C.P., who spoke on the Future of Physiotherapy. Other lecturers included Dr. Victor Dubowitz, Dr. Helen Dimsdale, Mr. Walpole Lewin, Mr A. J. Evans, and Dr. J. Delargy.

## UNSUITABLE FOR SCHOOL

THE procedure under the Education Act, 1944, for the care and training of mentally handicapped children will be modified by some sections of the new Mental Health Act which come into force on Nov. 1. In a circular to education authorities Sir David Eccles, the Minister of Education, says that they will extend the rights of parents, who will in future be able to require local education authorities to review, after a year, a decision that a child is unsuitable for education at school, and to appeal to the Minister on the result of the review. The procedure for arranging the medical examination of these children is simplified. New provisions are made to ensure consultation between education and health services; and the education authority, when they formally notify the parents that the child is unsuitable for an ordinary school, must now explain what the local health authority can do for his treatment, care, or training. Much of the success of the new arrangements will depend on cooperation between the health and education services, and the Minister considers that it would be helpful if the doctor who examines the child were acting for both authorities.

---

### University of London

Dr. R. J. Goldacre has been appointed to a readership in cell physiology tenable at the Institute of Cancer Research: Royal Cancer Hospital.

### University of Leeds

A series of lectures for registrars and senior house-officers will be held at the General Infirmary at Leeds at 5 P.M. and 6 P.M. on Wednesdays starting on Oct. 5. The speakers will include Miss U. M. Lister, Sir Andrew Claye, Mr. J. B. Farquhar, Mr. T. F. Redman, Mr. Herbert Agar, Mr. G. W. Theobald, Dr. R. R. Macdonald, and Mr. D. W. Currie. The fee for the series will be £3, and further information may be had from the sub-dean, School of Medicine, Thoresby Place, Leeds, 2.

### University of Glasgow

Dr. John Milne has been appointed McCall Anderson lecturer in dermatology. He will be in charge of the dermatological department at the Western Infirmary.

### World Health Organisation

Dr. Louis Verhoestraete has taken up his appointment as director of the division of health protection and promotion at W.H.O. headquarters in Geneva. This division, which was created recently in a reorganisation of the headquarters services, covers cancer, cardiovascular diseases, dental health, mental health, nutrition, and social and occupational health.

Dr. Verhoestraete has been chief of the health promotion branch of the Pan-American Sanitary Bureau in Washington, which is also a W.H.O. regional office, since 1954. He was born in 1912 in Belgium, and took his medical degree at the University of Louvain. From 1942 to 1947 he was a provincial adviser for the Œuvre Nationale de l'Enfance of Belgium. In 1947 he made a study tour in the United States, and the same year he joined W.H.O.'s staff as a consultant in pædiatrics with the United Nations Children's Fund in Paris. In 1950 he became chief of maternal and child health at W.H.O.'s Geneva headquarters. He received the degree of master of public health from Harvard University in 1954.

### Hospital Appointments in France

The Collège de Médecine des Hôpitaux de Paris has made arrangements for young doctors from other countries to hold junior hospital appointments in Paris.

The posts can be held for 1–3 years. The salaries and allowances paid are those of French *internes*. Candidates must have passed their qualifying examination in medicine and had 2 or 3 years' experience. They must also have a good knowledge of French. Applications are now invited for appointments for the year beginning Oct. 1, 1961. Further details can be had from the scientific office of the French Embassy, 22, Wilton Crescent, London, S.W.1.

### Royal Faculty of Physicians and Surgeons of Glasgow

At a meeting of the faculty on Sept. 5, the following were admitted to the fellowship:

Nalkunda Kyathappanavara Channappa, Gulamabbas Juma Ebrahim, Abraham Galea, A. J. Graham, J. A. Hynes, A. H. Laing, W. M. McCrae, Keshab Chandra Mallick, Tahir Abdel Mahmoud Rahman, *qua* physician; Abdul Khaliq, Badr Ul Islam Pirzada, W. H. Reid, *qua* surgeon.

A conference on accident surgery is to be held from Nov. 30 to Dec. 2 at the faculty, 242, St. Vincent Street, Glasgow, C.2. Particulars will be found in our advertisement columns.

### Institute of Diseases of the Chest, London

Clinical demonstrations for doctors will be arranged by Dr. Joseph Smart on Fridays from Sept. 30 to Dec. 16. Open lectures will be given on Wednesdays from Oct. 5 to Dec. 14 by Dr. J. R. Bignall, Dr. R. W. Riddell, Dr. V. Springett, Mr. O. S. Tubbs, Dr. W. D. W. Brooks, Dr. Paul Wood, Dr. J. N. Pattinson, Mr. T. Holmes Sellors, Dr. H. Nicholson, Mr. M. Paneth, and Dr. J. R. May. All the lectures will be held at 5 P.M. at the institute, Brompton Hospital, Fulham Road, S.W.3.

### British Postgraduate Medical Federation

The inaugural lecture of the 1960–61 series on the scientific basis of medicine will be given by Prof. C. H. Waddington at 5.30 P.M. on Thursday, Oct. 20, at the Senate House, University of London, Malet Street, W.C.1. His subject will be the significance of developmental biology.

---

A service for doctors is to be held in All Souls Church, Langham Place, London, W.1, on Sunday, Oct. 16, at 11 A.M. Sir Arthur Porritt and Sir James Paterson Ross will read the lessons. Doctors who wish to reserve seats for the service should write to the church secretary, who will also issue tickets (7*s*. 6*d*.) for a buffet lunch which is to be held after the service at the Royal Society of Medicine.

Mr. Leslie Farrer-Brown will give the inaugural address at the medical school, University of Birmingham, on Monday, Oct. 3, at 3 P.M.

The Chest and Heart Association is to hold a symposium on asthma on Wednesday, Nov. 2, at 4.30 P.M., in Edinburgh. Tickets (21*s*. each) may be had from the Association, 65, Castle Street, Edinburgh, 2.

A symposium on hæmatology for general practitioners is to be held at Addenbrooke's Hospital, Cambridge, on Saturday, Oct. 1. Further particulars may be had from the secretary of the Medical School, Tennis Court Road, Cambridge.

The Association of Clinical Biochemists and the Association of Clinical Pathologists will hold a scientific meeting on Saturday, Oct. 1, at 9.30 A.M., at the Royal College of Surgeons of England, Lincoln's Inn Fields, London, W.C.2. The meeting will include a symposium on malabsorption.

The next meeting of the Osler Club of London will take place on Tuesday, Oct. 11, at 8.15 P.M., at the British Museum, when Sir Frank Francis, Dr. W. S. C. Copeman, and Mr. W. T. Stearn will speak on Sir Hans Sloane.

The annual meeting of the North of England Otolaryngological Society will be held in Bolton on Saturday, Oct. 1, at 2 P.M.

Dr. G. R. Sharp has been appointed to an Imperial Chemical Industries fellowship to do research under Prof. C. F. W. Illingworth, Prof. R. C. Garry, and Dr. H. H. Pinkerton, on respiratory physiology and anæsthesia in the department of surgery at the Western Infirmary, Glasgow, where an oxygen pressure chamber has recently been installed.

The annual dinner for past and present students of the Middlesex Hospital Medical School will be held at the Savoy Hotel, London, W.C.2, on Friday, Sept. 30, at 7.30 P.M. A refresher course will be held on Friday and Saturday, Sept. 30 and Oct. 1, at the hospital. Further particulars may be had from the medical school secretary.

---

CORRIGENDUM: *Too Few Doctors*.—Our annotation of Sept. 3 said: "The Willink Committee suggested that the maximum list should be reduced without undue delay to 2500 in non-rural areas and to 2000 in rural areas." This was an incorrect reading of the committee's statement that "a realistic estimate of likely expansion over the next few years" would reduce the average numbers on doctors' lists to those figures. In the committee's view, 3500 persons on the list of a principal, plus 2000 where an assistant was employed, reflected the needs and conditions at the time when the committee met.